EBRUARY, 1942 Vol. 115, No. 2

ANNALS of SURGERY

A Monthly Review of Surgical Science and Practice

Included in This Issue

SYMPOSIUM ON THYROID

LATERAL ABERRANT THYROIDS *by* V. Kneeland Frantz, Richard Forsythe, John M. Hanford, William M. Rogers

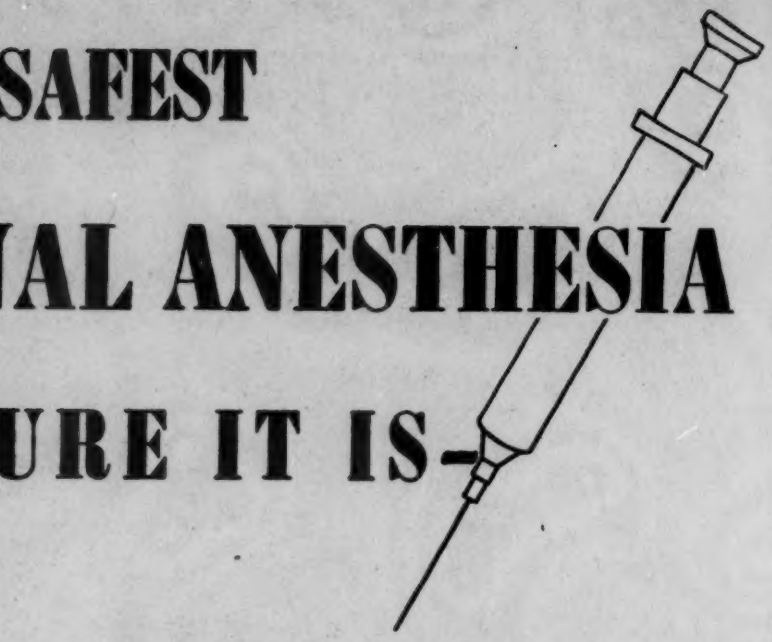
MASKED HYPERTHYROIDISM *by* Lester Breidenbach and Emanuel Appelbaum

END-RESULTS OF THYROIDECTOMY *by* Leonard Dobson, Hall Seely, Hugh Rose, Jr.

IODINE METABOLISM IN THYROID DISEASE *by* J. William Hinton, Edwin B. Eckerson, Maurice Bruger

J. B. LIPPINCOTT COMPANY

FOR SAFEST SPINAL ANESTHESIA BE SURE IT IS—



Many surgeons agree that NEOcaine is the simplest and safest of all spinal anesthetics.

NEOcaine is also simplest to use: After an ordinary lumbar puncture, you allow the spinal fluid to drop directly into the ampoule, quickly dissolving the crystals. Then you inject the solution slowly and keep the patient in the Trendelenburg position for three hours.

With this simple technique you produce satisfactory surgical anesthesia beginning in 5 to 10 minutes and lasting ordinarily 1 1/2 to 2 hours, longer with larger doses. Complete muscular relaxation facilitates delicate operative procedures. Recovery is rapid with minimum nausea.

Supplied in boxes of 10 ampoules of 50, 80, 100, 120, 150, 200 and 300 mg. of pure procaine hydrochloride, especially prepared for spinal anesthesia.

NEOCAINE

ANGLO-FRENCH LABORATORIES, INC.

75 VARICK ST. NEW YORK, N. Y.

ANNALS OF SURGERY

VOL. 115 FERRUARY, 1942 No. 2

LATERAL ABERRANT THYROIDS*

V. KNEELAND FRANTZ, M.D., RICHARD FORSYTHE, M.D.,
JOHN M. HANFORD, M.D., AND WILLIAM M. ROGERS, PH.D.
NEW YORK, N. Y.

FROM THE SURGICAL PATHOLOGY LABORATORY AND THE DEPARTMENT OF ANATOMY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, AND THE DEPARTMENT OF SURGERY, PRESBYTERIAN HOSPITAL, NEW YORK, N. Y.

IN PRESENTING another small group of cases of a relatively rare lesion, we have no desire to burden the literature with needless repetition. There has been, however, in recent publications, some difference of experience. Crile, 1939, made the following statements: "(1) Twenty cases of papillary carcinomas of the thyroid, 15 cases of papillary adenomas of the thyroid, and 13 cases of papillary tumors arising in lateral aberrant thyroid tissue are reported.

"(2) In only five of the 20 cases of papillary carcinoma of the thyroid has death occurred as a result of the tumor.

"(3) In no instance has it been proved that either regional or distant metastasis took place.

"(7) Tumors arising in lateral aberrant thyroid tissue are essentially benign. Only two of the 45 patients classified in the literature as having malignant tumors of lateral aberrant thyroid origin have been reported to have died as a result of recurrence of the tumor following operation. None of the 13 patients in this series has died as a result of lateral aberrant thyroid disease.

"It (8) has not been proved that either distant or local metastasis occurs from papillary tumors of lateral aberrant thyroid origin."

Lahey, Hare and Warren (1940) state that: "We have had 36 cases of malignancy of the lateral aberrant thyroid bodies in which operation was performed, and two patients have died of recurrence." Cohn and Stewart (1940) who report 16 cases of malignancy, state that: "Local or regional recurrence after incomplete operation occurred in 71 per cent of the cases of papillary tumor, but none of the patients with pure papillary tumors died of remote metastasis."

Ward (1940) on the other hand, reporting 12 cases of malignancy states that: "In this series, two deaths from papillary tumors occurred, one of

* Submitted for publication May 1, 1941.

these from pulmonary metastases, and I believe that a third death was caused by metastases from a lateral nonpapillary tumor. In view of these findings, I feel that a guarded prognosis should be given in similar cases, and that more deaths will be found in cases reported by other investigators if a sufficiently long period of observation is maintained."

Our own experience leads us to agree with Ward, and we wish to present it so that we may urge a serious surgical approach to what may appear at first study as a relatively benign lesion. At least some of the late, unexpected deaths we hope may be avoided if the problem is approached from this point of view. *Tumors in 27 of our 30 cases of lateral aberrant thyroid, malignant tumor in 23 of these 27, and eight deaths in these 23, or a 34 per cent mortality,* furnish the basis for our argument.

The term "aberrant thyroid" was first suggested by Schrager in 1906, and defined by him as "a mass of tissue having the structure of a normal or pathological thyroid gland and situated at some definite distance from the normal thyroid with which it has no connection whatsoever." Schrager gives credit to von Haller for first recognizing the condition in 1779, and the first adequate description was presented by Porta in 1849.

Distinction must be made between medial and lateral, as well as between true and false aberrant thyroid glands. It is accepted that medial aberrant thyroids are found along the thyroglossal tract, and these are not considered in this report. A false aberrant thyroid retains connection with the main gland—as a protrusion from it. This paper will be concerned only with true lateral aberrant thyroids.

Following Schrager's description, excellent summaries have been made by Billings and Paul (1925); Leech, Smith and Clute (1928); Dunhill (1931); Cattell (1931); Moritz and Bayless (1932); van den Wildenberg (1934); Crile (1939); Cohn and Stewart (1940); and Ward (1940). We have reviewed the literature to date and have been able to find 215 cases reported in detail. To this number must be added 36 reported by Lahey, Hare and Warren (1940), but these have not been analyzed. Of the 215 cases analyzed, 86 were considered definitely malignant. Of these, 66 were papillary tumors.

One of us (Rogers) has long been interested in the embryologic development of the thyroid, and it is worth a brief review, as it bears upon the surgical, anatomic and pathologic findings.

The description by His (1885) of the development of the human thyroid was accepted by anatomists as correct until it was contradicted by Grosser in 1910. His stated that the thyroid arose from three embryonic parts—one median anlage which developed from the floor of the pharynx and two lateral anlagen which arose from the last pharyngeal pouch. These three embryonic parts fused and developed into the thyroid gland.

Grosser thought the lateral thyroids, or ultimobranchial bodies, degenerated subsequent to their fusion with the median anlage. He consequently criticized the term lateral thyroid as being inaccurate.

In 1914, and again in 1939, Kingsbury agreed with Grosser, but stated that the human material available was not perfect for such a cytologic study. As a result his conclusions were made with reservations. In 1923, Kingsbury suggested a reinvestigation of the histogenesis of the thyroid on some mammal whose embryos could be attained in fresh condition. It was also necessary to have a large number of embryos of known ages to form a series of successively older stages.

In 1927, Rogers made a study of the histogenesis of the thyroid in the rat. This work was done in a closely graded series of approximately 300 embryos, fetuses and newborn animals. In this material mitoses and not degenerating cells were observed in the cell cords and masses derived from the ultimobranchial body. Since colloid-containing follicles developed in all of the cords in the region where the lateral thyroid was located, he concluded that the lateral thyroid (ultimobranchial body) formed some thyroid parenchyma which could not be distinguished histologically from any other part of the gland. In all probability the actual mass of thyroid tissue is relatively small.

Badertscher (1918), studying pig embryos and fetuses, had arrived at a similar conclusion. In 1933, Weller, studying human embryos, verified the above observations. However, we consider Weller's estimate, that the lateral thyroid contributes one-third of the tissue of the definitive thyroid, much too high. Norris (1937) considers that the lateral thyroid contributes about one-sixth to one-eighth of the thyroid parenchyma.

Rogers suggested that the strongly determined median thyroid cords might induce the less strongly determined lateral thyroid anlagen to develop into a greater amount of thyroid tissue than is the case when the two structures remain separate. Godwin (1937, 1939) endorsed this view as being highly probable.

True lateral aberrant thyroid masses do not necessarily represent the same embryologic material. For instance:

(a) In lingual thyroids any lateral aberrant thyroid tissue would be derived entirely from the lateral thyroid (ultimobranchial) bodies and would probably, though not necessarily, be associated with the parathyroid derived from the fourth pharyngeal pouch.

(b) In most instances lateral aberrant thyroids are derived from the lateral thyroid body, and cell cords from the lateral cornu of the median anlage which have fused together but have become separated from the main part of the median anlage.

A mechanical explanation for the failure of the lateral thyroid (Fig. 1) to descend is logical. The epithelial ductus pharyngobranchialis connecting the lateral thyroid with the pharynx may not rupture. Likewise the ectodermal cleft IV (ductus branchialis), which is fused to the fourth pouch, may also persist. Both of these structures are shown in Figure 1A in a human embryo of approximately six weeks (10.1 mm. in length).

The persistence of the ectodermal ductus branchialis after the rupture

of the entodermal ductus pharyngobranchialis probably explains the superficial position of our Case 3, where the tumor lay superficial to the first layer of deep fascia covering the sternocleidomastoid, but covered by the platysma, and possibly Case 12, although only the superficial part of this infiltrating growth was exposed. The platysma is derived from mesoderm of the hyoid arch, which grows downward and covers over the small third and fourth arches and their branchial ducts.

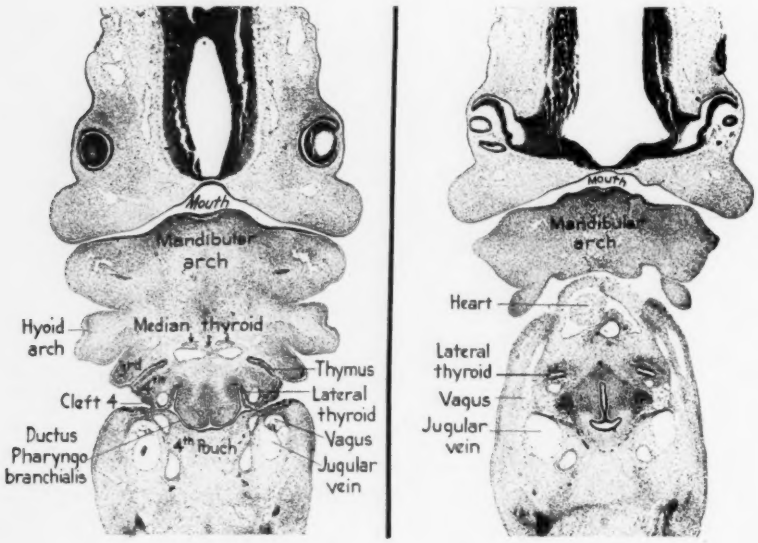


FIG. 1.—(A) A frontal section through the branchial region of a human embryo about six weeks of age (length 10.1 mm.), showing the four branchial arches and the ectodermal clefts which separate the arches from each other externally. The fourth pharyngeal pouch is in contact with the ectoderm of the fourth cleft. The entoderm of the dorsal part of this pouch will form the superior parathyroid. Extending caudally from the medial part of the fourth pouch is the lateral thyroid body. A part of the median thyroid is shown adjacent to the third aortic arch. (B) A section through the same embryo (17 sections ventral to Figure 1-A). It shows the lateral thyroid cut transversely.

Rarely is a lateral aberrant thyroid found above the level of the twelfth nerve in the submaxillary triangle. This is true because the median anlage does not expand laterally far enough to make contact with the lateral thyroid until it reaches this level in its descent. Since the lateral thyroid arises from the pharynx below the level of the twelfth nerve, tissue derived from this source must, of necessity, be located below this level.

It is easy to understand how loose cords or masses of thyroid tissue may be stranded along its descent from about the level of the junction of the common facial (or comparable vein) with the internal jugular vein down to the lower border of the thyroid gland, and intimately associated with the lymphoid tissue in this location. Most of these aberrant masses are related to the internal jugular vein or its tributaries which are close to the thyroid during its descent.

The relations of the medial and lateral thyroid components, the parathyroids and the thymus, to each other and to adjacent cervical structures in embryos of about seven weeks are shown in Figures 2 and 3. Lateral aberrant thyroids, occurring below the level of the thyroid, probably develop from thyroid cords which have come in contact with the thymus. Such masses may be deposited along the course taken by the descending thymus even as far caudal as the superior mediastinum. In Case 26, where a total thyroidectomy and bilateral neck dissection were performed, the patient, after some months, no longer required thyroid extract. It is possible in this case, therefore, that there is still functional thyroid tissue, and presumably this is in the superior mediastinum, the only region which has not been explored. The relations of the embryonic thymus are illustrated in Figure 2.

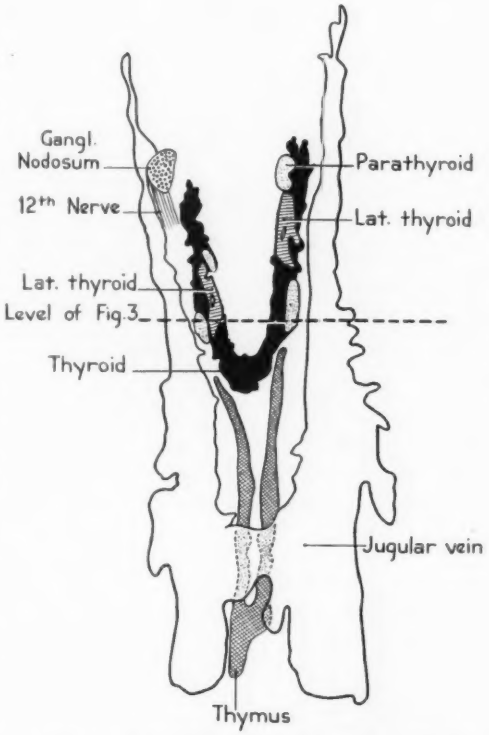


FIG. 2.—A reconstruction of the cervical region of a human embryo about seven weeks (length 22 mm.), illustrating the relative positions and sizes of the median and lateral thyroid bodies, the two pairs of parathyroids, the right and left thymus, the internal jugular veins, the 12th cranial nerve, and the ganglion nodosum of the vagus. The horizontal line represents the level of the section illustrated in Figure 3.

No experimental evidence has been introduced since this type of experimental embryology can not be undertaken on mammals. However, some natural experiments aid in understanding the rôle played by each component, but are not conclusive.

Cases have been reported in which myxedema followed removal of a lingual (medial) thyroid which had not fused with the lateral anlage—indicating that the maximum potentialities of the lateral anlagen do not materialize when fusion with the median thyroid fails to occur. Erdheim (1904) reported that in thyroaplasia the defect was of the middle anlage and that the lateral thyroid gave rise to no thyroid tissue. In Weller's myxedematous case (Ophelia P.), colloid-containing follicles definitely derived from the lateral thyroid are evidence that this embryonic part can and does produce thyroid-like follicles. Nor is there reason to doubt that the lateral as well as the median anlagen may be involved.

It is a curious fact, however, that there is no proof in man of function in lateral aberrant thyroids, and our Case 2, in which a toxic nodular thyroid

was removed, and the lateral aberrant tissue showed no evidences of hyperactivity, is of interest in this connection. Also, we have been unable to find in the literature a case in which removal of a lateral aberrant thyroid predisposed the patient to hypothyroidism. Probstein and Agress (1936) reported a case of myxedema following removal of an aberrant thyroid tumor. They were indefinite as to the exact location of the tumor, and from their de-

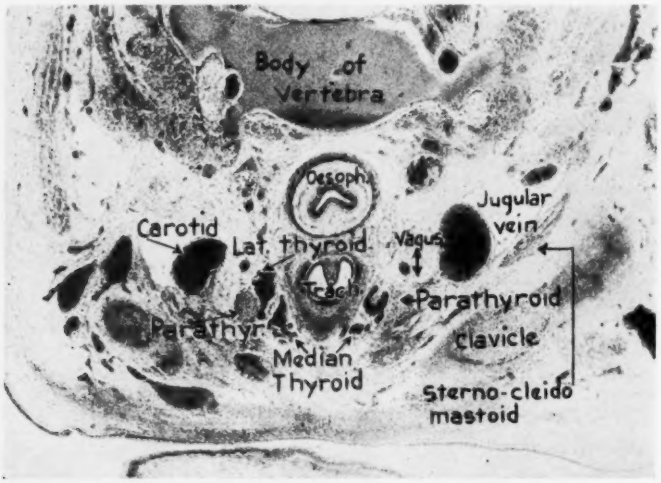


FIG. 3.—A transverse section through the cervical region of the embryo illustrated in Figure 2. On the right side the large lateral thyroid mass is intimately fused to the cords of the medial thyroid. The inferior parathyroids are present on both sides.

scription we believe that it should be regarded as a median aberrant thyroid. We encountered no cases of hyperthyroidism that were benefited by removal of lateral aberrant thyroid tissue alone. But it must be remembered that functional thyroid tissue is always present in the main gland.

Anatomically, as found at operation in our series, and as would be expected from a knowledge of the embryologic development, nearly all of the nodules lie beneath the sternocleidomastoid muscle. They may project from beneath the borders, and some are entirely behind the muscle in the posterior triangle, including the supraclavicular space. But they tend to occupy the same general location as the chain of deep cervical lymph nodes, from the posterior belly of the digastric muscle to the clavicle, none above the hypoglossal nerve. Except in advanced malignancy the lower nodules have been found lying loosely in areolar tissue from which they are easily shelled out, whereas the upper and midcervical nodules have more frequently been adherent to vein and muscle. The lowest nodule found lay below the lower pole of the thyroid gland. When the thyroid gland is involved with associated nodules these are found predominantly in the upper part of one lobe always on the affected side.

The diagram (Fig. 4) depicts a composite view of the location of all of the nodules, or groups of nodules in all of our cases, as if all were in the left side of the neck. Thus, it is found that the three dominant sites are: (1)

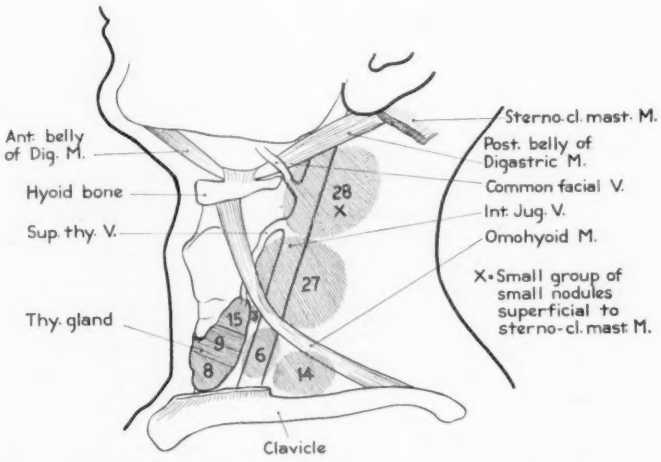


FIG. 4.—Diagram showing a composite view of the location of all of the nodules or groups of nodules in all of our cases, as if all were in the left side of the neck.

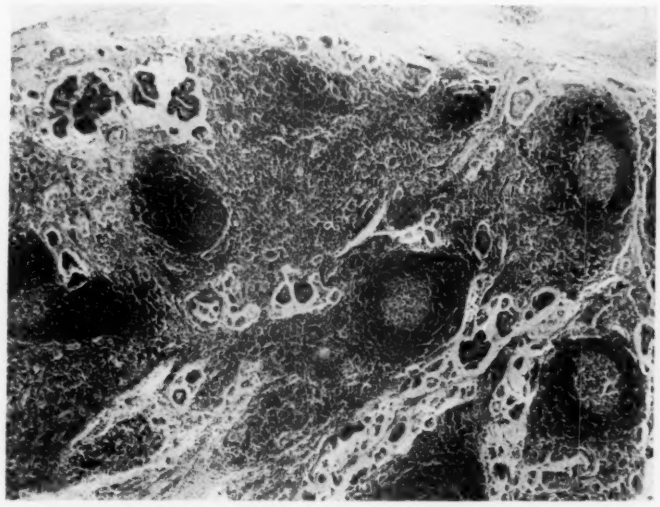


FIG. 5.—Photomicrograph from a case of papillary carcinoma of the main thyroid (with no lateral aberrant thyroid), showing multiple metastatic foci of papillary tumor scattered through a lymph node.

The upper deep cervical region, above the omohyoid muscle; (2) the lower deep cervical region, below the omohyoid muscle; (3) the supraclavicular region.

As we have said above, the malignancy of these tumors of lateral aberrant thyroids has been a matter of difference of opinion. In the literature we

were able to find only eight deaths reported—two by Dunhill (1931); one by Crile (1939); three by Ward (1940); and two by Lahey (1940). In only one of these was there definite evidence of distant metatases. Un-

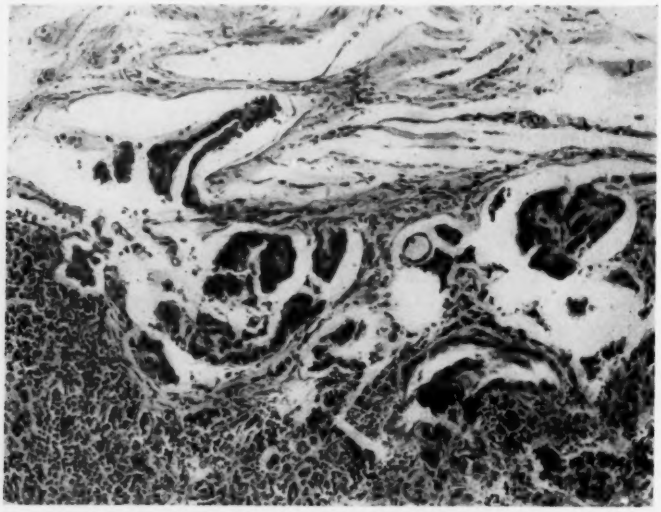


FIG. 6.—Photomicrograph of another lymph node from the same case as Figure 5, showing tumor in the afferent lymph vessel and in the marginal sinus.

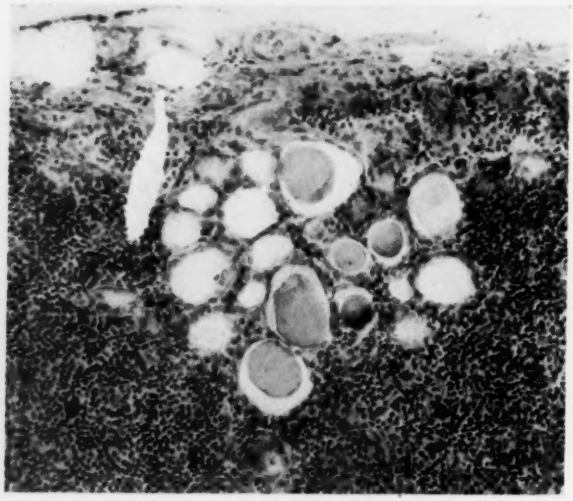


FIG. 7.—Case 1: Photomicrograph showing aberrant thyroid tissue in a lymph node.

fortunately, however, the majority of the reported cases lack follow-up data, and we wish later to emphasize that this is essential in order to determine the true nature of these tumors.

The distinction between lateral aberrant thyroid tumors and metastases to cervical lymph nodes from carcinoma of the thyroid is always difficult and at times impossible. In all our cases we have accepted metatases only when

groups of tumor cells lie scattered in a structure which has the architecture of a lymph node, *i.e.*, marginal sinus, sinusoids and lymph follicles. In Figures 5 and 6 the photomicrographs show such a metastasis, with papillary tumor not only in the marginal sinus and scattered through the sinusoids, but also in the afferent vessel leading to the node. Figure 7 from Case 1 shows what we consider aberrant thyroid tissue not occurring separately but situated in a lymph node. This being the case, if such a structure became neoplastic it would obviously be exceedingly difficult—really impossible—to differentiate between a primary tumor in a lymph node and a metastasis. Likewise, it is equally impossible to be certain whether an encapsulated nodule is a primary tumor, or a metastasis in a lymph node which has destroyed all the lymph node architecture. But we feel that multiple small foci in a lymph node are much more likely to represent metastases than to be multiple aberrant foci. Case 26 illustrates multiple aberrant thyroid nodules, bilateral, and also metastases.

The considerable number of cases recently reported attests the better recognition of the disease. Grueger (1876) states that in autopsy material a careful examination reveals aberrant thyroid tissue in 10 per cent of all cases. We know of no report since then in which the actual incidence of the anomaly is given. Lahey (1940) reports 36 cases of lateral aberrant thyroid carcinoma in 18,600 goiter operations at the Lahey Clinic, an incidence of approximately 0.2 per cent, and Crile, reporting the same series earlier gave an incidence of one lateral aberrant thyroid to 1,000 goiter operations. This undoubtedly includes the benign cases.

In a total of approximately 3,800 surgical thyroid specimens at the Presbyterian Hospital, from 1924 to January 1, 1941 of which 109 were carcinomas, we are presenting 30 cases of lateral aberrant thyroids. These, even if the main gland was also involved, are not included in the figure for the carcinomas given above. There were in this period also six cases of median aberrant thyroid tumors, and in the same period 39 thyroglossal cysts.

The difficulty in diagnosis reported in the literature has been present in our series. The commonest clinical picture is that of enlarged cervical lymph nodes. The following disease entities are, therefore, difficult to differentiate from lateral aberrant thyroids: Chronic lymphadenitis, tuberculous lymphadenitis, Hodgkin's disease, lymphosarcoma, metastatic carcinoma. Branchial cyst and carotid body tumor have also been confused. Even when the masses are exposed at operation the diagnosis may not be suspected unless they are strikingly bluish-black due to hemorrhage, which often occurs in the papillary tumors, or reddish enough to suggest normal thyroid tissue.

Our 30 cases have been classified as follows:

The six cases classified as adenocarcinoma all showed large undifferentiated areas, and two of them showed very striking spindle cell metaplasia.

It is not possible in the space allotted to analyze the case histories in detail. We regret this because we would like to present all the evidence upon which the diagnoses are based, realizing the controversial nature of this

material. We have scrutinized repeatedly the clinical, anatomic and pathologic features, and discarded all cases in which there could be any doubt as to the aberrant nature of the tissue. Summaries of the essential findings appear in the tables:

TABLE I

	No. of Cases	
Benign:		
Lateral aberrant thyroid gland	2	
Nontoxic nodular goiter of lateral aberrant thyroid	1	
Adenoma of lateral aberrant thyroid gland	1	
Papillary cysto-adenoma of lateral aberrant thyroid	3	
		7 (3 not neoplasms)
Malignant:		
Papillary carcinoma of lateral aberrant thyroid (thyroid involvement in all but three)	12	
Papillary- and adenoma malignum-type combined (both with thyroid involvement)	2	
Adenoma malignum-type, with no marked papillary arrangement (two with thyroid involvement and one without)	3	
Adenocarcinoma (thyroid involvement in four)	6	
		23 (12 predominantly papillary)

Table II summarizes the first three cases of the series which we do not regard as neoplasms. The first two are simple thyroid tissue without abnormality other than site, and were not recognized clinically or grossly, but were found on microscopic examination. Case 1 is illustrated in Figure 7. Case 2, as will be seen from the table, showed none of the histologic evidences of toxicity demonstrated in the main gland. Case 3 showed the same involutional changes in the aberrant nodule as, 11 years previously, were found in the main gland. Multiple lateral nodules had appeared in this case eight and one-half years after thyroidectomy, and one was removed for diagnosis. The remaining nodules have not changed clinically, but it has been decided to remove these in the near future because of the high incidence of neoplasm in these lateral masses.

TABLE II

LATERAL ABERRANT THYROIDS

Case No.	Age	Sex	Duration	Location	No. of Nodules	Condition of Thyroid Gland	Pathology	Treatment	Result
1	42	F.	?	? side	1	Nontoxic nodular goiter	Lat. aberrant thyroid tissue in lymph node	Excision	No recurrence 13 mos.
2	54	F.	?	? side	2	Toxic nodular goiter	Lat. aberrant thyroid tissue	Excision	No recurrence 75 mos.
3	25	F.	2 yrs.	Left	1	Thyroidectomy 11 yrs. prev., for nontoxic nodular goiter	Nontoxic goiter, lat. aberrant thyroid	Biopsy	Persistence of nodules not removed 17 mos. These to be removed

Table III is the analysis of the four cases thought to be benign neoplasms. Two cases originally included in this group are now classified as malignant, because recent operations for recurrence have demonstrated tumors, which, while still architecturally similar to the original growths, now have clear cut

FIG. 8.

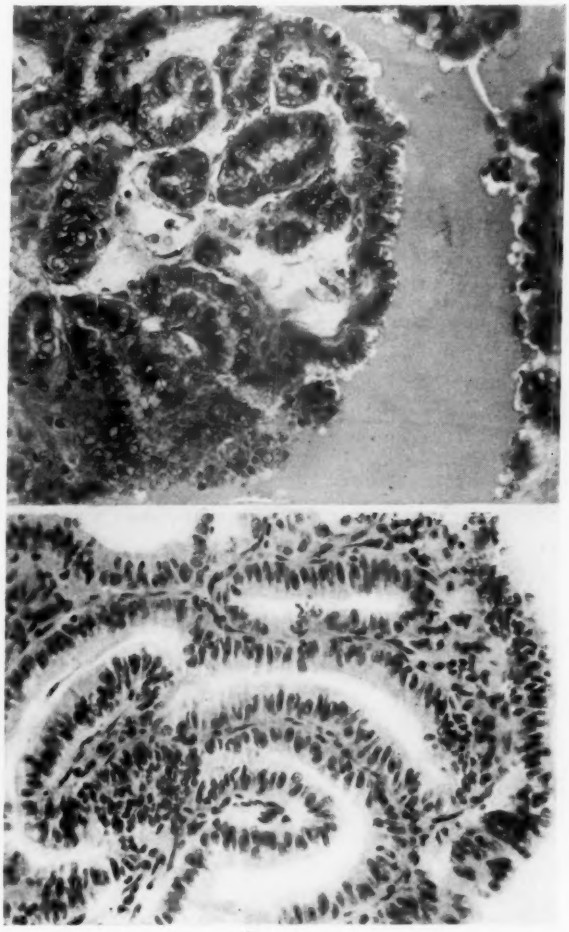


FIG. 9.

FIG. 8.—Case 6: Photomicrograph of a benign papillary cystoadenoma. This came from a single encapsulated mass. The patient is well, 52 months after operation.

FIG. 9.—Case 10: Photomicrograph of a papillary carcinoma of lateral aberrant thyroid. The main thyroid was involved in this case.

blood vessel invasion. One of these has been followed 11 years since the first procedure.

It is not impossible that a longer follow-up will prove us wrong on these four cases. The burden of proof is on the pathologist who calls any of these tumors benign. One must study the character of the cells, observe any nuclear

variation, search painstakingly for blood vessel and capsule invasion, and evaluate all these factors. Figure 8, Case 6, illustrates the histologic picture of a papillary cysto-adenoma which had only one excision, and no recurrence at 52 months. Case 4 of this group had had two previous operations for similar tumor, and Case 7 one previous operation. In neither of these cases was tumor found in the main gland, although Case 7 had a nontoxic nodular goiter. This case is the only one without a long follow-up, and has a persistent nodule which is to be removed shortly.

TABLE III

BENIGN TUMORS OF LATERAL ABERRANT THYROID

Case No.	Age	Sex	Duration	Location	No. of Nodules	Condition of Thyroid Gland	Pathology	Treatment	Result
4	52	F.	18 yrs.	Right	1	Not enlarged	Adenoma lat. ab. thy.	Excision	No recurrence 108 mos.
5	48	F.	13 yrs., 2 previous excisions elsewhere	Left	1	Not enlarged	Pap. cysto-adenoma lat. ab. thy.	Excision	No recurrence 101 mos.
6	53	F.	9 yrs.	Left	1	Not enlarged	Pap. cysto-adenoma lat. ab. thy.	Excision	No recurrence 52 mos.
7	40	F.	7 yrs., 1 previous excision	Right	4	Nontoxic nod. goiter	Pap. cysto-adenoma lat. ab. thy.	Excision	Persistent nodule 7 mos. To be removed

Table IV is the analysis of 12 cases of tumor thought to be malignant, and predominantly papillary. In these 12 cases the thyroid itself was involved in all but three, but in eight of the 12 the presenting symptom was the lateral mass. Two cases were bilateral, and these both had thyroid involvement. They were exceedingly well differentiated tumors, and this was striking in Case 10 (Fig. 9), where the metastasis in the lung (Fig. 10) has a most innocent appearance, reproducing the well-differentiated papillary character of the original growth. Presumably Crile would not classify any of these as papillary carcinoma for he states that: "A tumor which shows invasion of the blood vessels is here classified as a malignant adenoma even though it contains papillary areas," and "Invasion of blood vessels is rarely seen in tumors that are predominantly papillary." Much depends, of course, on one's interpretation of the word "predominantly," but in this group many sections were made of the tissue and the papillary arrangement was everywhere striking, even in the blood vessels (Fig. 11). Colloid was present in all but one of the tumors (this case had only a small biopsy) and psammomatous bodies in nine of the 11. Blood vessel invasion was twice not demonstrated. The material in the first of these was scanty, but the patient, Case 29, died of lung metastases. The other case without blood vessel invasion demonstrated is too recent to evaluate, having lived only 40 months after operation,

although still free from evidence of disease. In two the thyroid was not involved, and one of these, Case 29, already cited, died of local disease with

FIG. 10.—Case 10: Photomicrograph, high power, of lung metastasis, showing well-differentiated papillary tumor. (Section through the courtesy of Mt. Sinai Hospital.)

roentgenographic evidence of lung metastases, while the other, Case 9, has persistent local disease and roentgenographic evidence of pulmonary metastases.

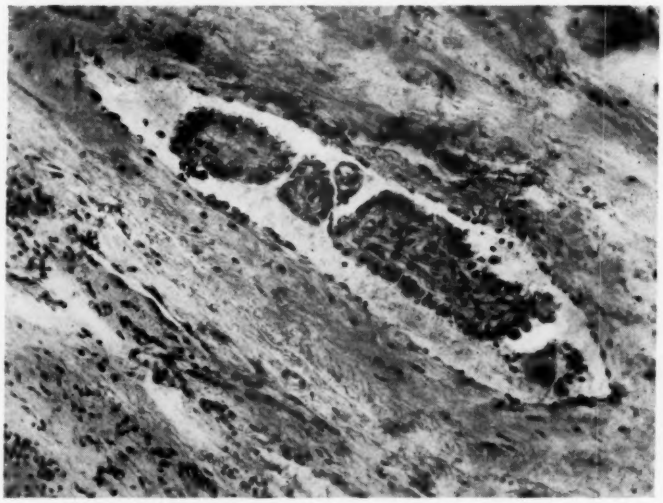


FIG. 11.—Case 15: Photomicrograph showing blood vessel invasion by well-differentiated papillary tumor.

Four of the cases had what we interpreted as lymph node metastases in addition to the aberrant nodules. One is dead. This is Case 10, with dis-

tant metastases demonstrated at autopsy. The other three are living (Cases 14, 15 and 16), one month, 24 months, and one month after their last operative procedures. All the cases with lymph node involvement showed blood vessel invasion.

Radiotherapy was employed in all four of the fatal cases—radium pack, radium needles and roentgenotherapy in the first, roentgenotherapy in the second and third, and radium needles and roentgenotherapy in the fourth. There was slight regression of the tumor in each case, but no arrest. One patient, who is still living, was treated intensively with roentgen-ray, a total of 13,240 r. to six fields before operation, with some regression at first. This case, No. 14, has required extensive surgery since then, and may well require more. One case, No. 9, had intensive radiation after biopsy, with temporary regression, but with recent increase in the size of the mass, and has recent roentgenographic evidence of lung metastases. Two other cases, Nos. 13 and 17, received intensive radiation after removal of the tumor. The effect of roentgenotherapy in these, therefore, cannot be judged, and they only have a short follow-up, but they are living without evidence of disease 40 and 12 months, respectively, after the last operation.

Table V is the analysis of 11 cases of malignant tumors not predominantly papillary. These are subdivided somewhat according to histologic appearance in Table II.

The first two cases, Nos. 20 and 21, were partly papillary, and also had large adenomatous areas resembling simple adenoma more than adenocarcinoma, or what we would call "carcinoma, adenoma malignum-type." One is living without evidence of disease 28 months after the second operation, and one without disease seven months after the third operation. Both showed some colloid acini. Both had blood vessel invasion. Neither had lymph node invasion. In both, the main gland was also involved. Both had radical surgery and radiation, the first had radiation before operation without effect, the second after removal of tumor, but a new nodule appeared during treatment.

The next three cases, Nos. 22, 23, and 24, were carcinoma, adenoma malignum-type, two with no papillary arrangement at all, and one with a very little. All showed colloid follicles. All had blood vessel invasion but no demonstrated lymph node metastases. One, Case 22, was radiated for recurrence and showed some regression but died with local disease. Case 24 lived 70 months, having had no postoperative radiation, and died without local recurrence but with roentgenographic evidence of metastases in vertebrae and lungs. This case was originally erroneously classified as simple adenoma.

Case 23 was originally classified as a simple adenoma, but was always under suspicion because she had a nodule in the main gland. This case had been followed for nearly 11 years after the first operation (she had a five-year history of tumor before operation), and her very recent exploration yielded a good-sized tumor still lateral, with marked blood vessel invasion.

The next six cases are arranged in order, as far as possible, according to the histologic evidence of differentiation. The first, No. 25 (Fig. 12), and

TABLE IV

MALIGNANT TUMORS OF LATERAL ABERRANT THYROID—PREDOMINANTLY PAPILLARY

Case No.	Age	Sex	Duration	Location	No. of Nodules	Condition of Thyroid Gland	Lateral Neck: Pathology	Treatment	Result
8	30	F.	18 mos.	Right	5	Not enlarged	Pap. carc. of lat. ab. thyroid	Excision. Second exc. 19 mos. later	Living without evidence of disease 19 mos. after 1st. op.; 2 wks. after 2nd op.
9	63	F.	24 mos.	Left	Several	Not enlarged	Pap. carc. of lat. ab. thyroid	Biopsy. X-ray	Living with local disease and lung met. 38 mos.
10	61	F.	6 mos.	Left	2 (3 lymph nodes)	Papillary carcinoma	Pap. carc. of lat. ab. thyroid. Met. to lymph nodes	Excision; thyroidectomy, x-ray and radium	Died lung and cerebral met. 111 mos. after 1st. op.
11	30	F.	14 mos.	Left	11	Papillary carcinoma	Pap. carc. of lat. ab. thyroid	Excision	No recurrence 64 mos.
12	40	M.	6 mos.	Right	1	Not enlarged	Pap. carc. of lat. ab. thyroid	Curettage and x-ray	Died 5 mos., with lung metastases
13	25	F.	5 yrs.	Right	6	Papillary carcinoma	Pap. carc. of lat. ab. thyroid	Excision; thyroidectomy, and x-ray	No recurrence 40 mos.
14	21	M.	2 wks.	Bilateral	19	Papillary carcinoma	Pap. carc. of lat. ab. thyroid. Met. to lymph nodes	Excision; thyroidectomy, and x-ray	No recur. 39 mos. after 1st. op., 1 mo. after 5th op.
15	17	M.	1 yr.	Left	7	Papillary carcinoma	Pap. carc. of lat. ab. thyroid. Met. to lymph nodes	Radical neck dissection. Thyroidectomy	No recur. 25 mos. after 1st. op., 24 mos. after 2nd op.
16	24	F.	20 mos.	Bilateral	24	Papillary carcinoma	Pap. carc. of lat. ab. thyroid. Met. to lymph nodes	Bilat. radical dissection and thyroidectomy. Exc. recurrent nodule	No recur. 12 mos. after 1st. op., 1 mo. after 2nd op.
17	42	F.	8 mos.	Right	2	Papillary carcinoma	Pap. carc. of lat. ab. thyroid	Excision; thyroidectomy, x-ray	No recurrence 12 mos.
18	50	M.	6 mos.	Right	Several	Papillary carcinoma	Pap. carc. of lat. ab. thyroid	Biopsy. Partial thyroidectomy; x-ray	Died 8 mos.; local disease
19	47	F.	12 mos.	Right	Several	Papillary carcinoma	Pap. carc. of lat. ab. thyroid	Biopsy. Partial thyroidectomy; radium and x-ray	Died 6 mos.; local disease

thought least undifferentiated, is dead of local disease. In this case the thyroid was not involved, and no blood vessel invasion was demonstrated; lymph node invasion, however, was seen. Roentgenotherapy caused only slight regression at first. Radical neck dissection also failed to control the disease.

The next case, No. 26, is the only child in the series. This case has already been published *in extenso* (Langman and Bruch) as a carcinoma with bilateral metastases. On reanalysis, however, we believe that, in addition, it represents

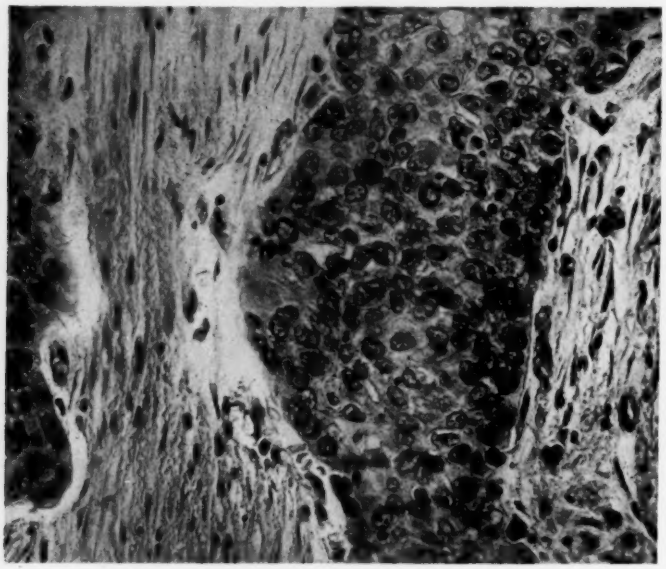


FIG. 12.—Case 25: Photomicrograph of biopsy specimen which was erroneously interpreted as squamous cell epithelioma.

bilateral carcinoma of aberrant thyroid, and as such, with a longer follow-up, should be included here. The disease in this child was very extensive, and was treated by radical surgery and postoperative radiation. She had a total thyroidectomy, bilateral radical neck dissection, and required thyroid extract, but it is of interest that she no longer requires this, suggesting that some thyroid tissue still remains. She is free from evidence of disease after 60 months.

Of the last four cases, one, Case 29, is dead with roentgenographic evidence of lung metastases, one, Case 27, is living with questionable recurrence locally, after 24 months, and two are living without evidence of disease, one, 118 months, and one, 28 months after their second operations, and one, 111 months. The one, Case 28, living 118 months, who was thought to have a highly malignant tumor (Fig. 13) had a biopsy, and three years later (because he failed to return for treatment) a partial thyroidectomy and excision of the lateral mass. Recurrence appeared after roentgenotherapy (6,000 r.), and was then apparently not controlled by insertion of needles (2,710 mg. hr.), so this was

TABLE V

MALIGNANT TUMORS OF LATERAL ABERRANT THYROID—NOT PREDOMINANTLY PAPILLARY

Case No.	Age	Sex	Duration	Location	No. of Nodules	Condition of Thyroid Gland	Lateral Neck: Pathology	Treatment	Result
20	60	M.	12 mos.	Left	1	Carcinoma	Carc. lat. ab. thy. Pap. and ad. malig.-type combined	(1) Part. thyroidectomy and excision (2) Excision. X-ray	No recur. or disease 38 mos. after 1st. op., 28 mos. after 2nd op.
21	35	F.	9 yrs.	Bilateral	6	Carcinoma	Carc. lat. ab. thy. Pap. and ad. malig.-type combined	Left. rad. dissect. Thyroidectomy. X-ray. Excision. Radium pack. X-ray	No recur. 16 mos. after 1st. op., 7 mos. after 3rd. op.
22	69	F.	25 yrs.	Left	1	Carcinoma	Carc. ad. malig.-type lat. ab. thy. (later primary ca. breast)	(1) Part. thyroidectomy (2) Excision	Dead with local disease, 92 mos.
23	16	F.	5 yrs.	Bilateral	9	Adenoma	Carc. lat. ab. thy., ad. malig.-type	Excision. Partial thyroidectomy. Exc. Recurrence	No recurrence 129 mos. after 1st. op., 1 mo. after 3rd op.
24	59	F.	35 yrs.	Right	6	Not enlarged	Carc. lat. ab. thy., ad. malig.-type	Excision	Died 94 mos. Met. to spine, lung
25	50	F.	12 mos.	Left	3	Not enlarged	Carc. lat. ab. thy. Met. to lymph nodes	Left rad. dissect. X-ray	Died 5 mos., local disease
26	4	F.	2 mos.	Bilateral	7 and many small	Carcinoma	Carc. lat. ab. thy. Met. to lymph nodes	In stages: Bilat. rad. dissect. Thyroidectomy, total. X-ray	No recur. 60 mos.
27	47	F.	?	Right	2	Carcinoma	Carc. lat. ab. thy.	Thyroidectomy. Excision. X-ray	? recurrence 24 mos.
28	50	M.	11 yrs.	Right	1	Carcinoma	Carc. lat. ab. thy.	Excision. Thyroidectomy. X-ray plus radium	No recur. 118 mos.
29	40	F.	7 yrs.	Left	4	Carcinoma	Carc. lat. ab. thy.	(1) Part. thyroidectomy (2) Excision	Died 16 mos., local disease. Lung met.
30	23	F.	24 mos.	Right	4	Not enlarged	Carc. lat. ab. thy. Met. to lymph nodes	Excision. X-ray	No recur. 38 mos. after 1st. op., 28 mos. after 2nd. op.

Volume 115
Number 2

followed by a radium pack of 25,000 mg. hr. Disease persisted and roentgenotherapy was again employed, and, with 5,100 r., the disease has appeared to be under control for the last seven years. This is the only case in the series which strongly suggests the roentgenotherapy has altered the course of the disease.*

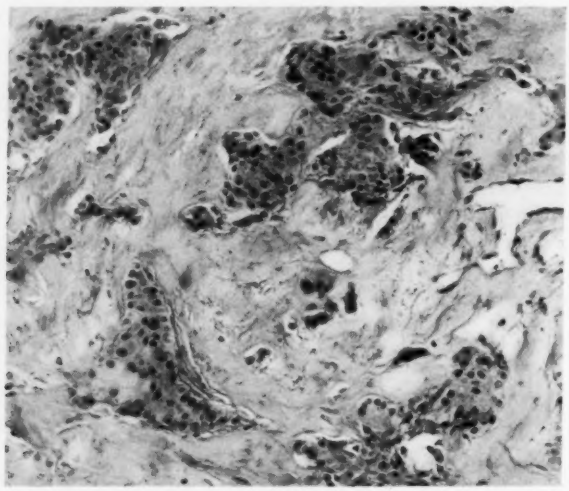


FIG. 13.—Case 28: Photomicrograph showing undifferentiated carcinoma with much fibrosis. This patient is well, 111 months after operation and roentgenotherapy for recurrence. He gave a history of tumor for 11 years before operation.

Discussion.—The group of benign cases is so small that no separate statistical summary is of interest. Certain findings may be stressed in the 23 malignant cases taken as a group.

There were 17 females and six males, a ratio of 2.8 to 1. There were four Negroes in the group.

The age on onset varied from four to 61. By decades the distribution is shown in Table VI:

TABLE VI

AGE OF ONSET BY DECADES

Decades	No. of Cases
1–10	1
11–20	2
21–30	8
31–40	3
41–50	6
51–60	1
61–70	2
Total	23

The basal metabolic rate was often not determined, and never of significance, except postoperatively in the one case with total thyroidectomy. There was no case of hyperthyroidism in the malignant group.

* The factors for roentgenotherapy were constant for all the cases. These were as follows: 200 K.V., 25 M. amps., 50 cm. T.S.D., with 1.05 mm. Cu. and 1.25 mm. Al. The single dose varied from 100 to 125 r.

In the malignant cases the presenting symptom was the lateral mass in 15, or 65 per cent. In this same group the thyroid gland was involved in 17 cases, or 74 per cent.

The malignant cases in which the thyroid was uninvolved are as follows:

(1) Papillary carcinoma. Dead, with persisting local disease and roentgenographic evidence of lung metastases.

(2) Papillary carcinoma. Living, with local disease and roentgenographic evidence of lung metastases.

(3) Papillary carcinoma. Living, without evidence of disease, 19 months after the first operation, two weeks after the second.

(4) Adenoma malignum. Dead, 94 months after operation, with no local recurrence but with roentgenographic evidence of metastases to vertebrae and lungs.

(5) Adenocarcinoma. Dead, five months after operation, of local disease.

(6) Adenocarcinoma. Living, without evidence of disease, 28 months after the second operation.

Lymph node involvement occurred in seven cases, or 30 per cent. In our series of 109 cases of carcinoma of the main gland there have been only four cases of regional lymph node metastases without lateral aberrant thyroid disease. Of these four cases, one is living without evidence of disease 63 months after partial thyroidectomy and excision of the metastatic nodes. This patient had a recurrence which has disappeared under roentgenotherapy. The other three all have persisting disease, six months, 64 months and 133 months, respectively. The patient who is living, without evidence of disease, may have had the course of the disease altered by roentgenotherapy, as this is at least a five-year arrest.

The statistics in the tables concerning the duration of the disease before and after operation should be noted carefully. It is obvious from these figures that long duration before, and *even after operation* is not necessarily an indication that the patient will not eventually succumb to the disease.

CONCLUSIONS

From this series we feel that it is evident that, even with careful laboratory study, it is difficult to differentiate between benign and malignant tumors in lateral aberrant thyroids. For this reason we advocate biopsy of one or more nodules with subsequent therapy dependent upon the laboratory report. If the biopsy shows a benign lesion, then an operation to remove all of the nodules is advised, because of the number of cases which give such a long history of stationary masses which subsequently proved to be carcinoma. It is, of course, impossible to know whether the histologic picture in these was the same from the onset of the swellings.

If the biopsy shows malignant disease with or without lymph node involvement, a radical neck dissection is advisable, on both sides if the disease is

bilateral. If the thyroid gland is involved, a partial or complete thyroidectomy is indicated, depending upon the findings.

There is not enough evidence to evaluate the effect of roentgenotherapy, but in at least two patients the disease appears to have been arrested by it. In others, recurrences appeared during treatment. It seems, therefore, a matter for personal decision in each individual case. It is the only therapeutic measure in the cases which, for one reason or another, are considered inoperable.

Finally, from the study of this series we feel justified in stating, emphatically, that all of these tumors should be considered potentially malignant, studied with care, treated radically, and followed indefinitely.

BIBLIOGRAPHY

d'Abreu, A. L.: The Significance of Lateral Aberrant Thyroids. Lancet, **2**, 1406, 1935.

Badertscher, J. A.: The Fate of the Ultimobranchial Bodies in the Pig (Sus scrofa). Am. J. Anat., **23**, 89, 1918.

Barker, A. E.: Cystic Accessory Thyroid Body. Tr. Path. Soc., London, **47**, 225, 1896.

Beeson, H. B.: Aberrant Goiter. Arch. Otolaryngol., **25**, 449, 1937.

Bérard, L., and Dunet, C.: Cancer Thyroïdien. Les Cancers Thyroïdien Aberrants. Chapter 6, p. 453. G. Doin, Paris, 1924.

Berry, J.: Diseases of the Thyroid Gland. Chapter 1, pp. 12, 15. P. Blakiston's Sons and Co., Philadelphia, 1901.

Billings, A. E., and Paul, J. R.: Tumors of Lateral Aberrant Thyroids. Bull. Ayer Clin. Lab., Pennsylvania Hospital, **9**, 27, 1925.

Binney, H.: Tumors of Aberrant Thyroids: Report of Case. Boston Med. and Surg. Jour., **190**, 227, 1924.

Cattell, R. B., and Hoover, W. B.: Lingual Thyroid Gland: Report of Case, and a Discussion of Aberrant Thyroid Tissue. Surg. Clin. North America, **9**, 1355, 1929.

Cattell, R. B.: Aberrant Thyroid. J.A.M.A., **97**, 1761, 1931.

Cattell, R. B.: Personal communication, 1940.

Champon: À Propos de Deux Goitres Kystiques Aberrants. Bull. Soc. belge d'otol. de rhino. et de laryngol., pp. 112–116, 1939.

Chwat, S.: Un Cas de Cancer de Thyroïde Aberrante Latérale. l'Oto-Rhino-Laryngologie Internationale, **52**, 65, 1937.

Clute, H. M., and Smith, L. W.: Cancer of the Thyroid Gland. Arch. Surg., **18**, 1, 1929.

Clute, H. M., and Warren, Shields: Cancer of the Thyroid Gland. Am. Jour. Cancer, **15**, 2563, 1931.

Cohn, L. C., and Stewart, G. A.: Tumors of the Lateral Thyroid Component. Arch. Surg., **40**, 585, 1940.

Cooke, A. B.: Aberrant Thyroid. California & West. Med., **37**, 47, 1932.

Crile, G. Jr.: Papillary Tumors of Thyroid and Lateral Aberrant Thyroid Origin, Surg., Gynec., and Obst., **69**, 39, 1939.

Crile, G., Jr.: Tumors of Lateral Aberrant Thyroid Origin. J.A.M.A., **113**, 1094, 1939.

Dunhill, T. P.: Carcinoma of the Thyroid Gland. Brit. Jour. Surg., **19**, 83, 1931.

Eberts, E. M.: Lateral Cervical Aberrant Thyroid. Canad. Med. Assn. Jour., **29**, 32, 1933.

Eerland, L. D., Nooster, H. H., Vos, J. J. T., Müller, H., and van der Horst, G. A.:

Over Struma Maligna in Nederlandsch Oost Indie. Geneesk. Tijdschr. v. Nederl., Indie, **75**, 184, 1935.

Erdheim, J.: I. Über Schildrusenaplasie. II. Geschwulste des Ductus thyreoglossus. III. Über einige menschliche Kiemenderivate. Beitr. z. path. Anat. u.z. all. Path. Bd. 35, S. 366–433, 1904.

Ewing, James: Neoplastic Diseases. Chapter 45, Tumors of the Thyroid, pp. 942. 3rd ed. W. B. Saunders Co., Philadelphia, 1928.

Forty, F.: Tumor of Aberrant Lateral Thyroid. Brit. Jour. Surg., **20**, 695, 1933.

Gaylord, H. R., and Marsh, M. C.: Carcinoma of the Thyroid in the Salmonoid Fishes. State Institute for the Study of Malignant Disease, Serial No. **99**, 373, 1914.

Geer, W. A.: Tumors of Lateral Aberrant Thyroid Tissue: Report of Two Cases. Conn. State M. J., **4**, 670–671, 1940.

Godwin, M. C.: Complex IV in the Dog: With Special Emphasis on the Relation of the Ultimobranchial Body to Interfollicular Cells in the Postnatal Thyroid Gland. Am. Jour. Anat., **60**, 299–339, 1937.

Godwin, M. C.: The Mammalian Thymus IV. The Development in the Dog. Am. J. Anat., **64**, 165, 1939.

Graham, Allen: Malignant Epithelial Tumors of the Thyroid. Surg., Gynec., and Obst., **39**, 781, 1924.

Grosser, Otto: Zur Kenntnis des ultimobranchialen Körpers beim Menschen. Anat. Anz., **37**, 337–342, 1910.

Greensfelder, Louis, and Bettman, R. S.: Carcinoma in Lateral Aberrant Thyroid Gland. J.A.M.A., **78**, 797, 1922.

Greteman, T. J., and Russum, B. C.: Aberrant Thyroid Tumors. Nebraska State Med. Jour., **21**, 384, 1936.

Grüber, Wensel: Anatomische Notizen: (1) Über die Glandula thyroidea Accessoria. Virchows Arch. f. path. Anat., **66**, 447, 1876.

Guazon, P.: Tumors from Aberrant Thyroid Tissue. Jour. Philippine Islands Med. Assn., **6**, 1, 1926.

Haagensen, C. D.: Cancer of the Thyroid: Its Radiosensitivity. Am. Jour. Cancer, **15** (suppl.), 2063, 1931.

Hameed, M. A.: Lateral Aberrant Thyroids. Brit. Med. Jour., **1**, 344, 1940.

Hanford, J. M.: Thyroid Nodules in the Lateral Neck Region. ANNALS OF SURGERY, **99**, 354, 1934.

Hare, H. F.: Cancer of the Thyroid in Children. Radiology, **28**, 131, 1937.

Hartley, J. N. J.: Some Errors in the Development of the Thyroid Gland. Surg., Gynec., and Obst., **35**, 543, 1922.

Hentz, V. C.: Lateral Aberrant Thyroid. Med. Rec., **142**, 416, 1935.

His, W.: Anatomie Menschlichen Embryonen. 1885, Leipzig.

Ho, K. H.: Carcinoma of Lateral Aberrant Thyroid: Report of Case. Southern Med. Jour., **32**, 1087, 1939.

Kamsler, A.: Carcinom einer akzessorischen Schilddrüse. Arch. f. klin. Chir., **127**, 624, 1923.

Kaplan, I. I.: Benign Metastatic Bone Involvement from Thyroid Tumors. Am. Jour. Surg., **23**, 559, 1934.

Keibel, Frank, and Mall, F. P.: Manual of Human Embryology. Chapter 17: The Development of the Pharynx and of the Organs of Respiration. P. 446, vol. 2. J. B. Lippincott Co., Philadelphia, 1912.

Kingsbury, B. F.: The Question of a Lateral Thyroid in Mammals: With Special Reference to Man. Am. Jour. Anat., **65**, 333, 1939.

Kingsbury, B. F.: On the so-called Ultimobranchial Body of the Mammalian Embryo: Man. Anat. Anz., **47**, 609, 1914.

Kingsbury, B. F.: The Development of the Human Pharynx. Am. J. Anat., **18**, 329, 1915.

Kingsbury, B. F.: A personal communication, 1923.

Lahey, F. H.: The Diagnosis and Management of Thyroid Conditions. Tr. West. Surg. Assn., 1934, p. 59.

Lahey, Frank H., Hare, Hugh F., and Warren, Shields: Carcinoma of the Thyroid. ANNALS OF SURGERY, **112**, 977–1005, 1940.

Langman, A. G., and Bruch, H.: Carcinoma of the Thyroid Gland in Children. Am. Jour. Dis. Child., **56**, 616–638, 1938.

Lawton, S. E.: Lateral Aberrant Thyroid Glands. Surg., Gynec., and Obst., **61**, 696, 1933.

Lazarus, J. A., and Rosenthal, A. A.: Lateral Aberrant Thyroid Glands. ANNALS OF SURGERY, **98**, 1023, 1933.

Leech, J. V., Smith, L. W., and Clute, H. M.: Aberrant Thyroid Glands. Am. Jour. Path., **4**, 481, 1928.

Lewisohn, Richard: Symmetrical Lateral Aberrant Thyroids. ANNALS OF SURGERY, **84**, 675, 1926.

Low, H. C.: Accessory Thyroid Glands. Boston Med. and Surg. Jour., **149**, 616, 1903.

MacCallum, W. G., and Fabyan, Marshall: On the Anatomy of a Myxoedematous Idiot. Bull. Johns Hopkins Hosp., **18**, 341, 1907.

Martin, J. D., and Elkin, D. C.: Hurthle Cell Tumors of the Thyroid. ANNALS OF SURGERY, **110**, 169, 1939.

Martin, Walton: Lateral Accessory Thyroid. ANNALS OF SURGERY, **60**, 379, 1914.

McGlannon, Alexis: Tumors of Lateral Aberrant Thyroid Tissue. Maryland Med. Jour., **51**, 7, 1908.

di Molfetta, N.: Di una Malformaziona Congenita della Ghiandola Tiroidea. Arch. ital. di chir., **51**, 680, 1938.

Moritz, A. R., and Bayless, Francis: Lateral Cervical Tumors of Aberrant Thyroid Tissue. Arch. Surg., **24**, 1028, 1932.

Moritz, A. R., and Bayless, Francis: Papilliferous Tumors of the Thyroid Gland and of Aberrant Thyroid Tissue. Am. Jour. Path., **7**, 675, 1931.

Morrin, F. J.: A Case of Bilateral Accessory Thyroids. Irish Jour. Med. Sci., **6**, 675, 1927.

Murphy, J. B.: Superior Accessory Thyroids. J.A.M.A., **45**, 1854, 1905.

Noordenbos, W.: Laterale Aberrante Schuldkliergezewellen. Nederl. Tijdschr. v. Geneesk, **78**, 2578, 1934.

Norris, E. H.: The Morphogenesis of the Follicles in the Human Thyroid Gland. Am. Jour. Anat., **20**, 411, 1916.

Norris, E. H.: The Parathyroid Glands and the Lateral Thyroid in Man: Their Morphogenesis, Histogenesis, Topographic Anatomy and Prenatal Growth. Publication Carnegie Inst., No. 479, Contribution to Embryology, No. 159, pp. 247–294, 1937.

Onufrio, Otto: Sarcoma Polimorfo-cellulare in Struma Aberrante Laterale. Arch. ital. di anat. Istologia Patologica, **5**, 935, 1934.

Paget, James: Lectures on Surgical Pathology, 3d ed., pp. 569–570, 1870. Longman, Green and Co., London.

Palitzer, G., and Hann, F.: Über die Entwicklung der branchiogenen Organe beim Menschen. Ztschr. f. Anat. u. Entirges., Bd. **104**, 670, 1935.

Paul, J. R.: Aberrant Thyroids. Atlantic Med. Jour., **29**, 684, 1926.

Pemberton, J. de J.: Treatment of Carcinoma of the Thyroid Gland. ANNALS OF SURGERY, **100**, 906, 1934.

Idem: Malignant Lesions of the Thyroid Gland: A Review of 774 Cases. Surg., Gynec., and Obst., **69**, 417, 1939.

Pool, E. H.: Carcinoma of an Accessory Thyroid. ANNALS OF SURGERY, **52**, 711, 1910.

Pollard, B.: Intracystic Papilloma of Accessory Thyroid Gland. Tr. Path. Soc., London, **37**, 507, 1886.

Porta, Luigi: Delle Malattie e delle Operazioni della ghiandola Tiroidea. Milano, 1849.

Portmann, U. V.: Malignant Tumors of the Thyroid Gland. Surg., Gynec., and Obst., **70,** 185, 1940.

Probstein, J. G., and Agress, Harry: Myxedema Following the Removal of an Aberrant Thyroid Tumor. New England Jour. Med., **214,** 1191, 1936.

Rogers, W. M.: The Fate of the Ultimobranchial Body in the White Rat. Am. Jour. Anat., **38,** 349, 1927.

Schmeisser, H. C.: Bilateral and Medial Aberrant Thyroid. Southern Med. Jour., **29,** 1174, 1936.

Schrager, V. L.: Lateral Aberrant Thyroids. Surg., Gynec., and Obstet., **3,** 465, 1906.

Simpson, W. M.: A Clinical and Pathological Study of 55 Malignant Neoplasms of the Thyroid Gland. Ann. Clin. Med., **4,** 643, 1926.

Sporn, Hyman, and Bolber, H.: An Unusual Location of an Aberrant Thyroid. Laryngoscope, **44,** 920, 1934.

Stout, A. P.: Human Cancer, Chapter 39, The Thyroid Gland, p. 839. Lea and Febiger, Philadelphia, 1932.

Tebbutt, A. H., and Woodhill, V. R.: Aberrant Thyroid Tissue. Med. Jour. Australia (suppl.), **12,** 358, 1927.

Tjokronegoro, Soetome: Enkele Waarnemingen Omtrent het Cystadenoma Papilliferum Thyroidea en de Struma Papillomatosa Lateralis (Ruhl). Geneesk, Tijdschr. v. Nederl.-Indie, **74,** 200, 1934.

Vidgoff, I. J.: Lateral Aberrant Thyroid. Western Jour. Surg., Obstet., and Gynec., **40,** 566, 1932.

Ward, Robertson: Relation of Tumors of Lateral Aberrant Thyroid Tissue to Malignant Disease of the Thyroid Gland. Arch. Surg., **40,** 606, 1940.

Warren, Shields: The Significance of Invasion of the Blood Vessels in Adenomas of the Thyroid Gland. Arch. Path., **11,** 255, 1931.

Watzka, M.: Vergleichende Untersuchengen über den ultimobranchialen Körper. Ztschr. f. Mikr.-anat. Forschung, Bd. **34,** 485, 1933.

Weller, G. L.: Development of the Thyroid, Parathyroid and Thymus Glands in Man. Contributions to Embryology, Carnegie Inst., Washington, **24,** 95, 1933.

Wohl, M. G.: Carcinoma of Lateral Aberrant Thyroid. Interstate Med. Jour., **24,** 1044, 1917.

van den Wildenberg, L.: Contribution à l'Étude des Thyroïdes Aberrantes Latérales. Les Ann. d'Oto-Laryng., **10,** 949, 1934.

van den Wildenberg, L., and Dupont, A.: À Propos des Glandes Thyroïdes Aberrantes Latérales. Rev. belge des Sci. Med., **3,** 827, 1931.

van den Wildenberg, L.: Les Erreurs de Diagnostie des Tumeurs Thyroïdienees. Bull. de l'Acad. roy. de Belgique, **13,** 420, 1933.

MASKED HYPERTHYROIDISM*

LESTER BREIDENBACH, M.D., AND EMANUEL APPELBAUM, M.D.
NEW YORK, N. Y.

GENERALLY SPEAKING, the diagnosis of frank hyperthyroidism of the exophthalmic type or the type associated with toxic adenoma of the thyroid gland, offers no particular difficulty. There are, however, patients suffering from thyrotoxicosis in whom the classic signs and symptoms of hyperthyroidism are either wanting or are not obvious. Such a person presents an atypical clinical picture of some other type of disease, such as organic heart disease accompanied by congestive heart failure, angina pectoris or auricular fibrillation, arterial hypertension, diabetes mellitus, gastro-intestinal disturbances, some form of malignancy, chronic pulmonary tuberculosis, psychoneurosis or some muscular disease. In these instances the thyrotoxicosis is either undiagnosed or diagnosed very late.

Marie,[1] as early as 1883, was perhaps the first to call attention to atypical hyperthyroidism. He stressed the importance of recognizing Basedow's disease with tremor and moderate tachycardia but without exophthalmos or goiter.

In 1885 Charcot,[2] under the caption *"Maladie de Basedow: formes frustes,"* drew attention to those cases of exophthalmic goiter in which one or the other of the triad of symptoms, struma, exophthalmos and tachycardia, was wanting. In 1889, he further elaborated upon cases of hyperthyroidism which failed to present the leading symptoms and labeled them as the attenuated form of the disease.

Levine and Sturgis,[3] in 1924, under the title "Hyperthyroidism Masked as Heart Disease," described five cases with symptoms referable to the heart, usually palpitation, pain, dyspnea and transient attacks of auricular fibrillation. Boas and Shapiro,[4] in 1925, discussed a group of cases of hyperthyroidism with hypertension which they regarded as a special syndrome to be distinguished from the ordinary form of hypertension and from exophthalmic goiter. Their patients showed an elevation of both the systolic and diastolic blood pressures, associated with cardiac hypertrophy. Hubbell,[5] in 1927, recorded two cases simulating diabetes mellitus. Levine and Walker,[6] in 1929, stressed the importance of recognizing latent hyperthyroidism in cases of auricular fibrillation which fail to respond to digitalis therapy. They mentioned also the fact that some of their patients with masked hyperthyroidism showed a transient glycosuria, mild persistent glycosuria, or an appreciable hypertension.

Hamburger and Lev,[7] in 1930, reported five cases of masked hyperthyroidism and reviewed the subject in a very comprehensive manner.

* Read before the New York Surgical Society, April 9, 1941.

They noted that their patients were all at or beyond the middle decade of life and that they did not present the usual obvious signs and symptoms of toxic goiter. The classical features of the disease were replaced by apathy, weakness, loss of weight, pigmentation, early fatigue, and some slight staring expression of the eyes; and in many instances by the clinical picture of some circulatory disorder; namely, congestive heart failure, auricular fibrillation, tachycardia, or angina pectoris. A lesser number presented the clinical picture of diabetes mellitus or of pernicious hyperemesis. Verbrycke,[8] in 1931, reported a series of 34 cases of hyperthyroidism masquerading as some form of gastro-intestinal disease. In 1931 and 1932, Lahey[9, 10, 11, 12] contributed an important series of papers on the subject. He called particular attention to an atypical form of the disease occurring in middle-aged or past middle-aged individuals, which he termed "apathetic hyperthyroidism."

Shorr[13] recently observed a group of cases of hyperthyroidism simulating myasthenia gravis or progressive muscular dystrophy. He emphasized that the muscular weakness in thyrotoxicosis, as well as in the muscular diseases, is the result of a defective creatine metabolism. In all these conditions creatine is excreted in abnormal amounts in the urine. However, by the use of iodine the creatine defect can be abolished in Graves' disease but not in muscular dystrophy or myasthenia gravis. Furthermore, the creatinuria of thyrotoxicosis is completely controlled following thyroidectomy.

It has seemed to us worth while to call attention again to the so-called masked hyperthyroidism, since the diagnosis of this form of the disease not infrequently passes unrecognized.

CASE REPORTS

Case 1.—A. F., male, age 60, was seen for the first time February 25, 1939. His main complaints were weakness, considerable loss of weight, precordial pain, and dyspnea on exertion. These symptoms began about a year and a half ago and became progressively more marked. The weakness progressed to the stage where he found it difficult to walk without tiring readily. He lost about 12 lbs. in the past three months.

His past history showed that he had been a diabetic of moderate severity for many years.

Examination showed the patient to be thin, almost emaciated, weighing 114 lbs. There was no exophthalmos. The neck was not enlarged and there was no evidence of an enlarged thyroid gland. The lungs were clear. The heart was not enlarged to percussion, but it had a rate of 116 to 120. There was also a short systolic murmur at the apex. Blood pressure 155/60. The abdomen and the extremities showed no abnormal findings. The reflexes were normal.

Gastro-intestinal and chest roentgenograms were entirely negative. The electrocardiogram did not show any remarkable changes. The urine showed a trace of sugar. The blood sugar was 155 and the cholesterol 250 mg. per cent. The blood CO_2 combining power was 54.1 per cent.

It was our impression that we were dealing here with a case of masked hyperthyroidism, *i.e.*, the hyperthyroidism was masquerading as a cardiac and/or some form of malignancy.

A basal metabolism determination was then made, which showed plus 50.

The patient was put to bed and given a high carbohydrate diet and insulin. He also received Lugol's solution, 10 minims three times a day. Within a relatively short time

he showed definite improvement. He began to gain weight and felt stronger. There was also a slowing of his heart rate with cessation of the precordial pain.

On May 23, 1939 he had a subtotal thyroidectomy performed. The pathologic diagnosis was that of colloid goiter suggesting the stage of regression in response to iodine therapy. Suggestion of previous toxicity was seen in one lobule.

The operation was followed almost immediately by very rapid and progressive improvement in his condition.

Examination on June 26 showed him to appear well nourished, with a weight of 138. His heart rate was 78. His blood pressure, however, remained elevated at 170/80. His diabetes was well under control. His basal metabolic rate was now plus 3. He had a sense of general well-being, and was entirely free from any symptoms. His present weight is 148.

Comment.—In this patient the outstanding symptoms were progressive weakness and loss of weight, precordial pain, and dyspnea. On examination there were none of the striking signs of hyperthyroidism except perhaps for a moderate tachycardia. He was for a long time considered to be a diabetic, complicated by coronary artery disease. Later in the course of his disease, in view of his persistent weight-loss, some form of malignancy was suspected. This was ruled out by radiographic studies. Indeed, the progressive asthenia and weight-loss in addition to the moderate tachycardia led to the diagnosis of hyperthyroidism. This was subsequently confirmed by the high basal metabolic rate and the therapeutic response to iodine medication. Following thyroidectomy, there was a complete recovery.

Case 2.—E. S., female, age 36, was admitted to Bellevue Hospital, March 31, 1939, with a complaint of "thumping of the heart" of two weeks' duration. The attacks would come on suddenly and were accompanied by cold sweats and a feeling of precordial discomfort. The episodes were usually of short duration. There was no dyspnea, cough or frank cardiac pain.

Her past history showed that she had had hypertension for about eight years. On several occasions she had symptoms referable to the hypertension, such as vertigo, headaches, vision disturbances, and epistaxis.

Physical examination showed the patient to be moderately pale and somewhat apprehensive. Her weight was 99 lbs. Temperature 100° F., pulse 140, respirations 20. There was no exophthalmos. The thyroid gland appeared palpable but not significantly enlarged. The lungs were clear. The heart was slightly enlarged, had a ringing aortic second sound and a rapid gallop rhythm. There were no murmurs. The heart rate could not be modified by pressure on either carotid sinus. Blood pressure 220/140. There was no tremor of the hands. The fundus examination showed moderately advanced hypertensive vascular changes.

The diagnosis on admission was essential hypertension and hypertensive heart disease. It could not be definitely determined, clinically, what form of tachycardia the patient had.

Several electrocardiograms were taken. Some showed runs of paroxysmal tachycardia of auricular origin but the majority showed a sinus tachycardia. Other changes noted in the tracings were depression of R-T 1 and 2 and inversion of T 1 and 2. Thus, there was evidence of some myocardial damage.

Several urine examinations were negative except for an occasional trace of albumin and a moderately low specific gravity. The blood chemistry was essentially normal. A roentgenogram showed the heart to be obliquely oval and the size and shape to be within normal limits. Roentgenograms of the kidneys did not show any evidence of calculi or of polycystic disease.

An attempt was made to control the tachycardia with digitalis, quinidine and also

ipecac, but without any success. The possibility of hyperthyroidism was, therefore, entertained. Several basal metabolism tests were then made and the readings ranged between plus 52 to plus 82.

It was our impression, therefore, that the patient had a masked form of hyperthyroidism associated with essential hypertension. She was, therefore, placed on a high caloric diet and Lugol's solution. On this regimen the patient showed some degree of improvement.

On June 1, 1939, under cyclopropane anesthesia, a subtotal thyroidectomy was performed.

The pathologic report on the removed thyroid gland was that of mild epithelial hyperplasia.

She had an uneventful convalescence and showed rapid, progressive improvement. Her heart rate became normal and has remained so. She has also gained 14 lbs. in weight. The basal metabolic rate was reduced to plus 0.9. Her hypertension, however, has persisted, although somewhat reduced.

Comment.—This patient on admission appeared to be a definite case of essential hypertension associated with hypertensive cardiopathy. The tachycardia, with symptoms referable to it, appeared to be one of the paroxysmal forms. There was nothing on admission to lead us to suspect the presence of an obscure thyroid disturbance. However, when the tachycardia failed to respond to medication, the presence of an underlying hyperthyroidism was suspected. This was confirmed by the repeated high basal metabolism rates. While following the Lugol regimen there was only slight improvement, the postoperative progress was rapid and most satisfactory. It is to be noted, however, that the hypertension persisted. This was attributed to the presence of an irreversible diffuse vascular disease. In this connection it will be recalled that Boas and Shapiro,[4] in 1925, reported a series of five cases presenting a diastolic hypertension with increased metabolism rate and concluded that such cases constituted a special syndrome.

Case 3.—A. S., female, age 59, was admitted to Sydenham Hospital, December 20, 1939, complaining of anorexia, flatulence, cardiac palpitation, nervousness, weakness, weight-loss, occasional dyspnea, slight swelling of the ankles, pain in the legs and arms and occasional sweating of the hands. These symptoms have lasted with remissions for more than five years and have become more pronounced and almost continuous during the past 10 days.

On examination, the patient appeared undernourished and apathetic. Her weight was 120 lbs. There was no exophthalmos and also the eye signs were negative. There was a slight enlargement of the left lobe and isthmus of the thyroid gland. There were a few moist and subcrepitant râles over the bases of both lungs. The heart was not enlarged and showed an irregular rhythm but no murmurs. The liver was felt one finger's-breadth below the costal border on the right side. The blood pressure was 200/60. There was a low-grade fever ranging between 99° and 101.6° F.

Examination of the urine showed a specific gravity of 1.012, a heavy trace of albumin and an occasional hyalin and granular cast. The phenolsulphonephthalein excretion was 15.5% in 2 hours. The blood urea was 17.5, and the cholesterol was 136 mg. per cent. The blood albumin was 3.9 and the globulin 2.6 Gm. per cent. A roentgenogram of the chest showed a generalized increase in the pulmonic markings and a heart of normal size. The electrocardiogram showed a QRS of low voltage and somewhat bizarre in the third lead, a depressed ST 4 segment, an inverted T 3 and auricular fibrillation. The basal metabolic rate was plus 71.

A diagnosis of hyperthyroidism was made and the patient was prepared for operation. On January 6, 1940, a left total thyroidectomy was performed. Except for an attack of bronchitis, the patient's postoperative course was uneventful. The blood pressure dropped to 135/80. The basal metabolic rate, however, was still plus 45.

The pathologic report on the specimen removed at operation was "microfollicular nodular goiter with degenerative changes."

The patient was readmitted to the hospital, April 28, 1940, for the purpose of operating upon the right side. Her general condition at that time was quite good. Two days later, five-sixths of the right lobe of the thyroid gland was removed.

The pathologic report on this specimen was "colloid involution stage of the thyroid."

A follow-up examination, September 16, 1940, showed the patient to be in excellent condition. Her weight was now 146½ lbs. The heart showed a regular sinus rhythm and a rate of 78. Blood pressure 150/90. The basal metabolic rate was plus 6.

Comment.—This patient was a typical example of the apathetic hyperthyroidism, as described by Lahey.[9] The outstanding complaints were weakness and weight-loss and symptoms referable to her heart. She was distinctly undernourished, and appeared apathetic. There was auricular fibrillation associated with congestive heart failure. These symptoms did not respond to the usual measures. These facts suggested an underlying thyrotoxicosis. There was also evidence of impairment of her kidneys which was unrelated to her thyrotoxicosis. The marked improvement in her condition and the relief of symptoms following operation were striking.

Case 4.—A. A., female, age 52, seen for the first time March 7, 1934, complained of cardiac palpitation, a "shaky feeling," shortness of breath and episodes of epigastric pain associated with vomiting of two years' duration. She was hospitalized several times during that period for purposes of observation but no definite diagnosis was established.

Physical examination showed a poorly nourished female, appearing apathetic. Weight 120 lbs. There was no exophthalmos. A small nodule was felt in the right lobe of the thyroid gland. The heart showed a slight enlargement to the left, a regular rhythm, and a rate of 96. Blood pressure 150/80. The lungs were clear. There was moderate tenderness in the epigastrium but no masses were felt. There was no tremor of the hands.

The basal metabolic rate was plus 38. A gastro-intestinal series, done previously, was reported to have shown hypermotility but no definite evidence of organic disease.

A diagnosis of hyperthyroidism was made and on March 3, a subtotal thyroidectomy was performed.

The removed specimen showed dilated acini lined by pale, cuboidal epithelium and filled with colloid. A few of the acini showed mild hyperplastic changes. In places, there was a mild lymphocytic infiltration.

Her recovery was uneventful, and she was discharged March 12, 1934.

She has been followed periodically during the past six years, during which period she has been in excellent health and entirely symptom-free. She has gained 24 lbs. in weight. Her heart rate is 76, and the basal metabolic rate varies from minus 10 to plus 4. Her blood pressure has remained 150/80.

Comment.—We considered this case also one of apathetic hyperthyroidism masquerading as a gastro-intestinal disease. There were, however, symptoms suggestive of impaired myocardial function. The persistent moderate tachycardia along with a small palpable nodule in the thyroid gland led us to suspect the possibility of a thyrotoxic factor. Except for the persistence of

the moderate hypertension, she has remained in excellent health following the operation.

Case 5.—M. R., female, married, age 56, when seen on February 2, 1940, complained of "nervous stomach," gas eructations, a smothering sensation and fainting spells of two years' duration. There was also cardiac palpitation, and loss of 15 lbs. in weight.

Examination revealed a poorly nourished female, appearing older than her age. Her weight was 111 lbs. The eyes were entirely normal. The neck showed an adenoma of about 2x3 cm. in the left upper lobs of the thyroid gland, which had never been noticed by the patient. This was completely hidden under the sternocleidomastoid muscle. The heart was not enlarged, and showed a regular rate of 100, and a faint systolic murmur at the apex. The liver was felt one finger's-breadth below the costal margin. Blood pressure 140/70. There was no tremor of her hands or tongue.

The electrocardiogram showed a regular sinus rhythm, a rate of 110 and no other abnormalities. Urine: Specific gravity 1.024, a faint trace of albumin, and 0.3% sugar. The basal metabolic rate was plus 26.

The moderate tachycardia, the weight-loss, and the presence of a small thyroid nodule suggested the diagnosis of thyrotoxicosis. Following the usual preoperative treatment, a subtotal thyroidectomy was performed on February 23.

The pathologic report showed a hyperplastic thyroid with colloid changes, probably due to iodine medication.

She made an uneventful recovery. At the time of her discharge on February 29, her weight was 120 lbs., the heart rate 78, and the basal metabolic rate minus 10.

A follow-up, May 31, 1940, showed the patient to be symptom-free. Weight was 128 lbs.; heart rate 80. The blood pressure remained unchanged, and her urine has been sugar-free since operation. Her blood sugar was 150 mg. per cent.

Comment.—This poorly nourished and senile-appearing patient was an instance of hyperthyroidism masked as a case of diabetes mellitus associated with nervousness. The presence of hyperthyroidism was suggested by the moderate tachycardia, weight-loss, and a thyroid nodule. There was a complete reversal of her symptoms following proper therapy.

Case 6.—S. C., male, age 58, entered Bellevue Hospital, May 9, 1939, complaining of pain over his precordium and left chest in the region of the scapula, pain over the lower back, weakness and cardiac palpitation of two weeks' duration. These symptoms became progressively more marked.

Examination revealed a well-developed, well-nourished, middle aged man. There was no enlargement of the thyroid gland. The lungs were clear. The heart was not enlarged, had sounds of good muscular quality, regular sinus rhythm, and a rate varying from 90 to 120. Blood pressure 156/92. The impression was that the patient had arteriosclerotic heart disease.

The electrocardiogram showed severe myocardial changes suggestive of infarction of the posterior basal portion of the left ventricle.

The patient was treated with bed rest and digitalis. After a period of three weeks he left the hospital contrary to the advice of the staff.

The patient was readmitted to the hospital June 7, 1939. His complaints were similar to those of his first admission; namely, severe pain over the precordium and also pain in the back and marked weakness. In addition, he noted, also, swelling of his ankles.

Examination now showed an emaciated, white male, appearing chronically ill. He was extremely restless and uncooperative. There was definite dyspnea, orthopnea and moderate cyanosis. There was no enlargement of the thyroid gland, no exophthalmos and no tremor of the tongue or hands. There was, however, bilateral ankle edema. The lungs showed numerous moist râles at both bases. The heart showed very distant

sounds, had a regular rhythm and a rate of 124. Blood pressure 124/76. It was felt that the patient had a severe form of arteriosclerotic heart disease. The marked emaciation and the tachycardia suggested also the possibility of a hyperthyroidism.

The basal metabolic rate was plus 117. The blood chemistry showed a cholesterol of 148, sugar 87, nonprotein nitrogen 39, and uric acid 3 mg. per 100 cc. A roentgenogram of the heart did not show any enlargement. The electrocardiogram showed a sinus tachycardia and evidence of moderate myocardial damage.

After 15 days' preparation a right hemisubtotal thyroidectomy was performed, June 28, 1939. There was a decided improvement in the clinical condition following this operation.

On July 11, 1939, a left lobe subtotal thyroidectomy was performed. His postoperative course was uneventful, and his improvement progressive. There was a complete change in the clinical picture. The patient gained weight, was cheerful and cooperative. The basal metabolic rate was now plus 12. He was discharged, August 13, 1939, in excellent condition, having gained 27 lbs.

The pathologic diagnosis of the right lobe was a hyperplastic goiter and the left lobe was that of a colloid goiter with a few intravesicular papillary projections.

Comment.—While it is our feeling that this patient undoubtedly had some myocardial damage suggestive of a posterior basal infarct he suffered also from a severe form of thyrotoxicosis. His failure to respond adequately to bed rest and digitalis, the emaciation and persistent tachycardia suggested a diagnosis of hyperthyroidism, which was confirmed by the unusually high basal metabolic rate. It is to be noted, also, that in this instance the cholesterol was markedly reduced. The thyrotoxicosis unquestionably increased the severity of the associated heart disease. The patient's recovery following operation was little short of astounding.

Case 7.—B. S., male, age 62, when seen, April 2, 1932, complained of abdominal pain, slight diarrhea of eight months' duration. For the past month he also had precordial pain, and had lost 16 lbs. The abdominal pain which was localized in the epigastrium, would occur about one hour after eating and was relieved by food.

Physical examination revealed an elderly, undernourished apathetic patient, appearing chronically ill. There was no exophthalmos but a slight stare. The isthmus of the thyroid gland was palpable. The lungs showed moist râles at both bases. The heart was not enlarged and had a rapid irregular rhythm. There were no murmurs. There was a pulse deficit of 24. Blood pressure 110/60. The abdomen was slightly distended and showed marked tenderness in the epigastrium. The liver edge was felt two fingers'-breadth below the costal margin. There was pretibial edema.

The electrocardiogram showed auricular fibrillation. A roentgenogram of the gastrointestinal tract showed a persistent deformity of the duodenal bulb, indicative of duodenal ulcer.

The patient was put on an ulcer regimen, and he improved promptly. The abdominal pain disappeared and the diarrhea stopped. He also gained several pounds in weight.

This improvement, however, was only temporary, and within two months, most, if not all, of his original symptoms returned. He developed in addition a severe cough productive of blood-streaked expectoration.

During the following two years the clinical course was progressively downward with an occasional remission in his symptoms. In view of his asthenia, weight-loss, and cough with blood-streaked sputum, it was deemed advisable to investigate the patient from the standpoint of pulmonary tuberculosis. Accordingly, he was hospitalized for a period of three weeks. The physical findings were essentially those previously recorded.

Gastro-intestinal roentgenograms showed, now, overactivity of the duodenal cap but

not a persistent defect. This suggested the possible presence of a duodenal ulcer but was not conclusive. The roentgenogram of the lungs suggested the presence of a small amount of infiltration in the right apex and of old tuberculous emphysematous bullae in both upper lobes and diaphragmatic adhesions on both sides. The sputum was negative for tubercle bacilli. Two basal metabolic rate tests showed plus 26 and plus 36, respectively.

It was thought, now, that the patient had hyperthyroidism, and that this was responsible for his symptoms of asthenia, weight-loss, epigastric pain and congestive heart failure with auricular fibrillation which failed to respond to digitalis. Following a 12-day period of preparation with Lugol's solution, there was a marked improvement in all his symptoms.

On March 3, 1934, a subtotal thyroidectomy was performed. Prompt improvement followed operation. At the time of his discharge from the hospital, March 27, he was symptom-free and showed a gain in weight of 5 lbs. His heart showed a regular sinus rhythm and a rate of 72. The basal metabolic rate was plus 8.

The pathologic diagnosis of the removed gland was colloid adenoma of the thyroid gland with several scattered areas of typical hyperplasia with intravesicular papillary projections.

Comment.—The patient during the different stages of his clinical course was considered to have peptic ulcer, pulmonary tuberculosis and heart disease. Not only the clinical findings but also the laboratory data supported, to a certain extent, these various diagnoses. Indeed, it required repeated roentgenographic studies to rule out the presence of duodenal ulcer and of active pulmonary tuberculosis. Persistence of his asthenia, of his epigastric pains, and the weight-loss, in addition to the auricular fibrillation and congestive heart failure, which failed to respond to digitalis, suggested, finally, the diagnosis of hyperthyroidism. This was confirmed by a moderate increase in his basal metabolic rate and a definite improvement following Lugol therapy. Operation resulted in a complete, permanent recovery, with a total disappearance of all gastro-intestinal and cardiac symptoms.

Case 8.—M. C., female, age 35, seen for the first time June 22, 1939, complained of cardiac palpitation, considerable loss of weight, swelling of the feet, slight cough, occasional hemoptysis, and epistaxis of two years' duration. At one time during this period tuberculosis was suspected but was ruled out by the negative physical findings, negative sputum and negative roentgenologic studies.

Physical examination showed an emaciated young female, appearing chronically ill. There was no exophthalmos. The isthmus of the thyroid was just barely palpable but there was no discernible enlargement of either lobe. The lungs showed moist râles at both bases. The heart was not enlarged to percussion, had a regular rhythm and a rate of 120. There were no murmurs. The liver was felt two fingers'-breadth below the costal margin and was slightly tender. There was slight pretibial edema. The hands were not moist and showed a very slight tremor. Blood pressure 180/100. Fluoroscopy showed the lungs to be clear and the heart to be of normal size and shape. There was no evidence of a substernal goiter.

A diagnosis of hyperthyroidism was made and the patient was hospitalized. Following 11 days' preoperative therapy with bed rest, high calory diet and Lugol's solution, a definite improvement occurred. On July 4, 1939, a subtotal thyroidectomy was performed. The postoperative course was uneventful. The patient was discharged, July 12, 1939, in excellent condition.

The pathologic diagnosis of the thyroid removed at the operation was hyperplastic goiter.

A follow-up examination, August 14, 1939, showed the patient to be symptom-free. Her weight was 123 lbs. The heart rate was 78 and the blood pressure 140/70. The basal metabolic rate was minus 13.

Comment.—In this case the diagnosis of pulmonary tuberculosis was entertained for awhile, because of the hemoptysis and persistent weight-loss. This diagnosis, however, was definitely ruled out by sputum examination and roentgenographic study of the lungs. Subsequently, the patient presented symptoms of congestive heart failure. In the absence of pulmonary tuberculosis, the presence of tachycardia and weight-loss led to the diagnosis of hyperthyroidism. Relief resulted after a diagnosis had been established from the administration of Lugol's solution and thyroidectomy.

Case 9.—Z. J., female, age 65, when first seen April 1, 1932, complained of nonproductive cough, dyspnea, substernal distress, cardiac palpitation and weakness of one year's duration. She had been, also, a mild diabetic of many years' standing.

Physical examination revealed a small, fairly well-nourished elderly female, weighing 126 lbs. The eyes showed no exophthalmos. The thyroid gland was neither enlarged nor palpable. The lungs were clear. The heart was not enlarged to percussion and had no murmurs. The rhythm was regular and the rate was 88. Blood pressure 140/80. Urine: Specific gravity 1.020, negative for albumin and sugar. Blood sugar 100 mg. per 100 cc.

She was kept under observation for a period of two years, during which time the clinical picture remained unchanged.

On May 31, 1934, she complained of progressive weakness and moderate weight-loss. Pulse 96, blood pressure 170/70. Weight 111 lbs. The urine showed 1.5% sugar, blood sugar 150 mg. per cent. A roentgenogram of the chest showed a small substernal goiter. The basal metabolic rate was plus 66. This established the diagnosis of hyperthyroidism.

Following iodine therapy, the patient showed a gain of 3 lbs. in weight, a drop of pulse rate to 78, and blood pressure 140/80, and a reduction in the basal metabolic rate to plus 38.

A subtotal thyroidectomy was performed June 13, 1934. Except for the development of auricular fibrillation which lasted eight days, her postoperative course was smooth, and her recovery was complete.

The pathologic report on the removed specimen was adenoma of the thyroid gland with moderate hyperplastic changes and vesicles filled with colloid. The diagnosis was toxic adenoma.

When followed up, July 26, 1936, the patient was in excellent condition. Her weight was 130 lbs., the heart was regular and had a rate of 78. Blood pressure 110/60, basal metabolic rate minus 10. Blood sugar 120 mg. per 100 cc., and the urine was sugar-free.

Comment.—This is an instance of hyperthyroidism masquerading as diabetes mellitus, associated with angina pectoris. While progressive weakness in the presence of diabetes of only moderate severity aroused some suspicion, the diagnosis of hyperthyroidism was not seriously considered until a substernal goiter was discovered roentgenologically. Thyroidectomy resulted in marked improvement in the clinical picture including the diabetic state.

Case 10.—O. U., female, age 66, when seen, March 9, 1940, complained of dizzy spells, weakness, cardiac palpitation and orthopnea of three years' duration. There was a

slight loss of weight. These symptoms were aggravated during the past month, following an attack of grippe. Her past history revealed that she had had hypertension since 1929. In 1938 she was treated for cardiac decompensation.

Physical examination showed a well-developed female, moderately emaciated and dyspneic. Her weight was 116 lbs. There was no exophthalmos. On palpation of the thyroid gland one could feel the isthmus and a small nodule of about 2 cm. in diameter in each lateral lobe. The heart was enlarged to the left, had an irregular rhythm and a rate of about 120. There was a pulse deficit of 22. The aortic second sound was markedly accentuated. A loud systolic murmur was heard all over the precordium. Blood pressure 204/120. The liver was tender and was palpable three fingers'-breadth below the costal border. There was no tremor.

The blood cholesterol was 200 mg. per cent. The basal metabolic rate was plus 58. The electrocardiogram showed left axis deviation but no other striking changes. The urine was essentially negative.

A diagnosis of hyperthyroidism was made. The patient was hospitalized, March 10, 1940, and was treated for 12 days with Lugol's solution. The basal metabolic rate dropped to plus 22.

On March 21, a subtotal thyroidectomy was performed. Her convalescence was uneventful and her recovery complete.

The pathologic diagnosis was toxic adenomata with colloid changes.

A check-up on September 21, showed a regular heart rate of 80 and a blood pressure of 160/100. Weight 135 lbs. Basal metabolic rate plus 6. She had, now, a glycosuria and a blood sugar or 197 mg. per cent.

Comment.—This case represents the typical thyrocardiac in which symptoms of myocardial failure were predominant. The presence of thyrotoxicosis was entertained because of the weakness, weight-loss and the rapid irregular rhythm suggestive of auricular fibrillation. The symptoms were entirely relieved by a compound solution of iodine and thyroidectomy. It is to be noted that the irregular rhythm which appeared to be that of auricular fibrillation cleared up following the administration of iodine. Unfortunately, no electrocardiogram was made of the arrhythmia. Although there was a temporary improvement in the hypertension, it did not persist. This is not uncommon, as has been pointed out by Boas and Shapiro.[4] It is to be noted, also, that diabetes occurred following thyroidectomy. The significance of this is difficult to determine.

Case 11.—G. W., female, age 39, when first seen June 1, 1938, complained of thumping in the head and pain in the back of the neck, nervousness, cardiac palpitation and precordial pain of three months' duration. There was also a considerable loss of weight over a period of several years, from 161 to 128 lbs.

Physical examination revealed a fairly well-nourished female who did not appear chronically ill. The eyes showed no exophthalmos. The thyroid gland was slightly enlarged and smooth. The heart was not enlarged, had a normal rhythm and a rate of 90. Blood pressure 150/90. The lungs were clear. There was no tremor. Basal metabolic rate plus 33.

A diagnosis of hyperthyroidism was made and the patient was hospitalized, June 15, 1938. Following an eight-day period of preparation with Lugol's solution, the patient was anesthetized with avertin-cyclopropane anesthesia which resulted in an acceleration of the heart rate to 130 and an irregular rhythm. The operation was, therefore, deferred. Following three more days of preparation, a subtotal thyroidectomy was performed.

The patient made an uneventful recovery and was discharged from the hospital, June 30, 1938, at which time her heart rate was 72, and the blood pressure 120/70. She was entirely symptom-free.

Pathologic examination of the glandular tissue removed showed acini with frank hyperplastic changes. There was an unusual degree of lymphatic infiltration, both diffusely and in aggregations. The findings were those of mixed hyperplastic and colloid goiter.

A follow-up, March 8, 1939, showed the patient to be in excellent condition and entirely free from symptoms. Weight 138 lbs.; heart rate around 70. Basal metabolic rate minus 5.

Comment.—This case is an example of hyperthyroidism resembling a neurasthenic state. Indeed, it would have been difficult to attribute her symptoms definitely to thyrotoxicosis if it were not for the very decided improvement which followed the use of Lugol's solution, and particularly after thyroidectomy.

Case 12.—M. O., male, age 55, when seen, October 19, 1940, complained of anorexia, loss of 40 lbs. in weight, and diarrhea of six weeks' duration. There were also attacks of abdominal colic, and on a few occasions episodes of vomiting. There was occasional cardiac palpitation. His previous history was entirely negative.

Examination showed a well-developed male, looking rather chronically ill. There was no exophthalmos and, indeed, the eyes seemed sunken in appearance. The thyroid gland could not be felt. The heart was not enlarged, had a regular rhythm and had a rate of 88. There was a short systolic murmur at the apex. The lungs were entirely clear. The abdomen was scaphoid and presented no masses. There was, however, some tenderness in the epigastrium. The liver and spleen were not felt. The hands showed a very fine tremor. Weight 156 lbs. Blood pressure 150/90.

The gastro-intestinal series was entirely negative. The basal metabolic rate was plus 48. A definite diagnosis of hyperthyroidism was made. The patient was then prepared for operation by administering Lugol's solution from October 29 to November 11. Following this regimen his weight increased to 165 lbs., the diarrhea stopped, and his appetite improved.

On November 13, 1940, a subtotal thyroidectomy was performed. His recovery was uneventful, and he was discharged from the hospital, November 20, 1940.

The pathologic diagnosis of the removed gland was mixed hyperplastic goiter.

Comment.—This represents a case of thyrotoxicosis masked as some form of gastro-intestinal disease. No pathology in the gastro-intestinal tract was found roentgenologically. The presence of a fine tremor of the hands led us to suspect hyperthyroidism as the cause of his gastro-intestinal manifestations. Prompt and marked improvement followed the employment of Lugol's solution and thyroidectomy.

COMMENT.—The term masked hyperthyroidism applied to this series of patients connotes that the evidence of thyrotoxicosis is obscured by symptoms and signs of other clinical entities. As shown in Table I, the usual obvious signs and symptoms of toxic goiter were not present at all, or only to a slight degree. For purpose of classification the cases fall into groups depending upon the clinical entities which they resemble. This grouping is shown in Table II. In most instances the patient presented more than one clinical pattern.

TABLE I

SYMPTOMS AND SIGNS IN 12 INSTANCES OF MASKED HYPERTHYROIDISM

Case No.	Sex	Age	Exop.	Goiter	Tachy.	Tremor	Nervousness	Sweating	Dyspnea	Palpable	Cong. Heart Failure	Aur. Fib.	Precord. Pain	Vomiting	Diarrhea	Ab. Pain	Anorexia	Wt. Loss	Weakness	Blood Pressure	Glycosuria	B.M.R.
1	M.	60	—	—	—	—	—	—	—	+	—	—	—	+	+	+	+	+	+	155/60	+	+50
2	F.	30	—	—	Mod.	—	—	Sl.	+	+	+	+	—	—	—	—	—	+	+	220/140	—	+82
3	F.	59	—	Very sl.	Marked	—	+	—	+	+	—	—	—	—	—	+	—	+	+	200/60	—	+71
4	F.	52	—	Sl. Nodule	—	—	—	—	+	+	+	—	—	—	—	—	—	+	+	150/80	—	+38
5	F.	56	—	Nodule	Sl.	—	+	—	+	+	+	—	+	—	—	—	—	+	+	140/70	+	+20
6	M.	58	—	—	Mod.	—	—	—	+	+	+	—	+	—	—	—	—	+	+	156/92	—	+117
7	M.	62	Sl. stare	—	+	—	—	—	+	+	+	—	+	—	—	—	—	+	+	110/60	—	+36
8	F.	35	—	—	Mod.	Sl.	—	—	+	+	+	—	+	—	—	—	—	+	+	180/100	—	+54
9	F.	65	—	—	—	—	—	—	+	+	—	—	—	—	—	—	—	+	+	140/80	+	+66
10	F.	66	—	Mod.	Mod.	—	—	—	+	+	—	—	—	—	—	—	—	+	+	204/120	—	+58
11	F.	39	—	Sl.	—	—	—	—	—	—	—	—	—	—	—	—	—	+	—	150/90	—	+33
12	M.	55	—	—	—	Sl.	—	—	—	+	—	—	—	—	—	—	—	+	+	150/90	—	+48

TABLE II

GROUPING ACCORDING TO SIMULATED ENTITIES

	Simulated Diseases	Number of Cases
I.	Heart diseases	9
II.	Gastro-intestinal disturbance	4
III.	Diabetes mellitus	3
IV.	Hypertension	2
V.	Neurosis	2
VI.	Pulmonary tuberculosis	2

By far the largest and most important group was that in which there was present a clinical picture of some circulatory disorder; namely, congestive heart failure, auricular fibrillation, tachycardia, or angina pectoris. Nine of our patients showed symptoms and signs of circulatory disorder. The most frequent symptom was cardiac palpitation, being noted in seven instances. Definite signs of congestive heart failure were present in five of the cases. Dyspnea was the outstanding symptom in five instances. Four of the patients presented an anginal syndrome. Auricular fibrillation was noted in three instances. In one patient marked tachycardia was the outstanding symptom.

Two of the patients (Cases 3 and 7) with congestive heart failure and auricular fibrillation showed a striking degree of apathy. They were similar to the group of cases, "Apathetic Hyperthyroidism," described by Lahey.[9] Undoubtedly, the patients with congestive heart failure, with or without auricular fibrillation, had preexisting organic heart disease, largely of the arteriosclerotic type. It is our belief, also, that the patients with angina pectoris suffered from pathologic hearts on the basis of coronary artery disease. Indeed, in one case (Case 6) with congestive heart failure and angina, definite signs of myocardial infarction were noted in the electrocardiogram. As pointed out by Hamburger and Lev,[7] these cases might be regarded as instances of latent angina pectoris, in whom the thyrotoxicosis served to convert their latent angina to an active one because of the burden it imposes.

In four instances the patients presented symptoms referable to the gastro-intestinal tract. These included anorexia, vomiting, abdominal pain and diarrhea. The additional symptoms of weight-loss and asthenia in two of the cases suggested a diagnosis of some form of gastro-intestinal malignancy. In one instance the diagnosis of peptic ulcer was entertained because of the definite time relationship of the pain to meals and relief by food. Indeed, in this case the roentgenogram showed hyperperistalsis of the duodenum but no persistent defect. It should be noted that subtotal thyroidectomy completely relieved these various complaints.

In three instances the hyperthyroidism was masked by diabetes mellitus, which was only of moderate severity and persisted even after thyroidectomy. In this connection it should be noted that there is a definite disturbance of carbohydrate metabolism in about 3.5 per cent of the cases of hyperthyroidism. This disturbance bears no relation to the severity of the hyperthyroidism. The storage mechanism of glycogen in the liver appears to be impaired. However, it is not the liver alone which is responsible for the carbohydrate

metabolism disturbance, for when the patient recovers from the hyperthyroidism, he still remains a diabetic.

The usual form of hypertension found in hyperthyroidism is a moderate elevation of the systolic without a corresponding rise in the diastolic pressure. There are, however, instances with pronounced elevation in both systolic and diastolic pressures. In these cases an underlying hyperthyroidism may be entirely obscured by the hypertension, which, as a rule, persists even after thyroidectomy. This was observed in two of our cases (Cases 2 and 10). It is probable that these patients have an associated essential hypertension or some form of diffuse vascular disease. In this connection, it will be recalled that Boas and Shapiro[4] regarded a group of cases of hyperthyroidism with diastolic hypertension as a special syndrome to be distinguished from the ordinary form of hypertension and from exophthalmic goiter.

Hyperthyroidism associated with symptoms of neurasthenia or symptoms suggesting pulmonary tuberculosis, was more difficult to recognize. In these instances a long period of clinical observation and careful evaluation of suggestive signs made the diagnosis possible.

While these various types of masked hyperthyroidism are the only ones that we have encountered, there are, undoubtedly, other forms which with further study will come to light. We have already referred to a group which masquerades as progressive muscular dystrophy or myasthenia gravis. As emphasized by Hamburger and Lev,[7] these cases of masked hyperthyroidism "are important because of the difficulty of recognizing them, because of their frequency and, particularly, because of the brilliant results that are obtainable by correct diagnosis and treatment."

Summary and Conclusions

(1) We have presented a series of 12 cases of masked hyperthyroidism, dividing them into groups depending upon the clinical entities which they resemble.

(2) Great emphasis was laid on the importance of bearing in mind the possibility of thyrotoxicosis when a patient presents an atypical clinical picture of some other type of disease, particularly organic heart disease, with or without congestive heart failure, angina pectoris or auricular fibrillation, diabetes mellitus, hypertension, some form of gastro-intestinal disturbance, or a psychoneurosis.

(3) It was pointed out that the diagnosis of masked hyperthyroidism, in addition to the points mentioned, was based on certain suggestive signs and symptoms as persistent moderate tachycardia, unexplained weight-loss, an increase in the basal metabolic rate, improvement or relief of symptoms, decrease in the basal metabolic rate following iodine medication and thyroidectomy, and, finally, the histologic report of the removed gland.

(4) We have stressed the importance of recognizing this frequently misdiagnosed group of cases because of their relative frequency and particularly because of the brilliant results that follow surgical treatment.

REFERENCES

[1] Marie, P.: Contribution à l'étude et du diagnostic des formes frustes de la maladie de Basedow, Paris thèses, 1883.

[2] Charcot, J. M.: Maladie de Basedow: formes frustes; nouveau signe physique; traitement par l'électricité. Gaz. d'hôp., No. 13, 15, January 31, 1885.

Idem: Les formes frustes du goitre exophthalmique. Gaz. d'hôp. Par., **62,** 315, 1889.

[3] Levine, S. A., and Sturgis, C. C.: Hyperthyroidism Masked as Heart Disease. Boston Med. and Surg. Jour., **190,** 233, February 14, 1924.

[4] Boas, E. P., and Shapiro, S.: Diastolic Hypertension with Increased Basal Metabolic Rate. J.A.M.A., **84,** 1558–1561, May 23, 1925.

[5] Hubbell, R. J.: Hyperthyroidism Masked by the Diabetic Syndrome. Jour. of Michigan Med. Soc., **26,** 311, May, 1927.

[6] Levine, S. A., and Walker, G. S.: Further Observations on Latent Hyperthyroidism Masked as Heart Disease: Angina Pectoris. New England Med. Jour., **210,** 1020–1030, November 21, 1929.

[7] Hamburger, W. W., and Lev, M. W.: Masked Hyperthyroidism. J.A.M.A., **94,** 2050, June 28, 1930.

[8] Verbrycke, J. R.: Masked Gastro-intestinal Hyperthyroidism: Report of 34 Cases. J.A.M.A., **97,** 513, August 22, 1931.

[9] Lahey, F. H.: Nonactivated (Apathetic) Type of Hyperthyroidism. New England Jour. Med., **204,** 747–748, April 9, 1931.

[10] Lahey, F. H.: Apathetic Thyroidism. ANNALS OF SURGERY, **92,** 1026, May, 1931.

[11] Lahey, F. H.: The Management of Severe and of Atypical Hyperthyroidism. Annals of Int. Med., **5,** 1123, March, 1932.

[12] Lahey, F. H.: Activated and Apathetic Hyperthyroidism: Their Importance in Cases of Heart Failure. South. Surgeon, **1,** 36–38, April, 1932.

[13] Shorr, E.: Personal communication to authors.

THE END-RESULTS OF THYROIDECTOMY

LEONARD DOBSON, M.D.,
HALL SEELY, M.D.,
AND
HUGH ROSE, JR., M.D.
SAN FRANCISCO, CALIF.

FOREWORD BY EMILE HOLMAN, M.D.

FROM THE POSTOPERATIVE THYROID CLINIC, MEDICAL AND SURGICAL SERVICES, STANFORD UNIVERSITY MEDICAL SCHOOL, SAN FRANCISCO, CALIF.

FOREWORD

A FRANK, detailed, honestly compiled presentation of results in a fairly standardized surgical procedure is a most wholesome exercise for any surgeon, but particularly advantageous for the young surgeons in training. As stated by the authors, most of the thyroidectomies included in this series were performed by the resident surgeons, whose periods of training before their residency ranged from three to five years.

The survey, conducted carefully over a period of years, disclosed a very definite improvement in mortality and morbidity in the latter half of the series, an improvement which may well be attributed to the application of lessons learned from a critical analysis of current experiences, from which all members of the staff benefited. Such studies should be included as part of the regular training of the resident staff.

There have been relatively few reports of the end-results of thyroidectomy from nonendemic goiterous regions. We wish to present the results obtained in 341 consecutive patients operated upon for disease of the thyroid in the Clinic Service of the Stanford University Hospital. The shortest period of observation is six months, and the longest 13 years. Particular attention was paid to a study of the postoperative complications.

The types of cases encountered in this series are classified in Table I:

TABLE I

CLASSIFICATION OF TYPES OF THYROID DISEASE ANALYSED

Type	Female	Male	Total
Diffuse toxic goiter	116	41	157
Adenoma:			
Nontoxic	66	12	78
Toxic	69	6	75
Colloid goiter	15	..	15
Chronic thyroiditis	7	..	7
Tuberculosis	..	1	1
Neoplastic:			
Benign (fibroma)	1	..	1
Carcinoma	3	3	6
Lingual	1	..	1
Totals	278	63	341

Preoperative Treatment.—All of the patients with hyperthyroidism, either mild or severe, were admitted to the Medical Service for preparation before surgery. Patients in whom there was no evidence of hyperthyroidism were usually admitted directly to the Surgical Service. On the Medical Service a fairly standardized treatment was instituted, the main variation being its duration before operation. Bed rest, preferably in a room apart from the ward, was imposed. A high caloric (3,500 calories daily) high vitamin diet was administered, supplemented by vitamin concentrates. Fluids were given as desired except two hours before operation when 1,000 cc. of 10 per cent glucose in normal salt solution was administered intravenously. One-half grain of phenobarbital was given routinely three or four times daily. Any patients showing signs of cardiac failure were treated accordingly. Iodine (in some form) was given to all toxic patients, by far the most common preparation being Lugol's solution, ten drops thrice daily. The period over which this treatment was kept up varied from ten days to one month. There was no evidence that continuation of the treatment for more than ten days to two weeks brought on "iodine escape," and in a few of the patients who did not do so well postoperatively we thought the amount of iodine inadequate. The patients who had been treated with iodine intermittently or who had had iodine continuously for a long time prior to hospital entry usually did not respond as well as those who had had no iodine, and consequently a longer period of bed rest before operation was required.

The basal metabolic rate was determined on entry before treatment was started and every few days thereafter until the operation was performed. Blood, urine, stool and Wassermann reaction were studied. A roentgenogram of the chest was made to show the size of the heart, the condition of the lungs, and the possible presence of a substernal thyroid. Electrocardiograms were taken routinely. Determinations of the blood cholesterol were made routinely at first, but recently were omitted, because the information obtained was not very helpful. Studies of the creatine and creatinine in the urine seem to be of more value. The larynx was routinely examined before operation to note the motility of the vocal cords.

The criteria of improvement and of readiness of the patient for operation were: (1) The decrease or disappearance of the patient's symptoms; (2) the lowering of the pulse rate; and (3) the lowering of the basal metabolic rate. There was no limit set to which the pulse rate and basal metabolic rate must fall, but it was not until both of these had dropped to a stationary level and remained there for several days that the patient was considered ready for operation.

Operative Technic.—Silk technic, without drainage, has been employed since 1925 in all operations performed under the supervision of Dr. Emile Holman. In most of the adenomata, mildly toxic or nontoxic, a subtotal thyroidectomy was performed, leaving a fairly liberal portion of the gland. Subtotal thyroidectomies, leaving only a very small portion of the gland, were undertaken in the toxic, diffuse goiters and in the severely toxic adenomata.

The majority of the thyroidectomies were performed by the resident surgeon, some of the more seriously toxic patients being operated upon by the staff. Twenty-three surgeons operated upon these patients during this period.

The technic of subtotal thyroidectomy as used in most of the cases was that taught the resident surgeon by the visiting staff, and consisted substantially as follows: The anesthesia employed in practically all cases was nitrous oxide and oxygen, preceded in recent cases by avertin. Several cases were operated upon entirely under local anesthesia supplemented occasionally by avertin.

A short, low incision was made in the folds of the skin 2-3 cm. above the suprasternal notch. The incision was carried through the skin, and platysma muscle. The bleeding points were tied with fine silk. The upper flap was dissected to the lower border of the thyroid cartilage and the lower flap to the manubrium. A vertical incision was made in the middle cervical fascia down to the isthmus or trachea, the prethyroid muscle, the sternohyoid, the sternothyroid; and the omohyoid muscles were retracted laterally, the sternohyoid and sternothyroid muscles being first separated by blunt dissection. Only rarely, in very large glands, was it necessary to divide the middle cervical fascia and prethyroid muscles to obtain exposure. The thyroid was exposed by displacing the sternothyroid muscle laterally and the extracapsular areolar tissue by blunt dissection. The right superior pole of the gland was exposed; and the superior thyroid artery and vein isolated by blunt dissection and doubly clamped. The vessels were cut between the clamps and doubly ligated with double medium silk. The superior pole was retracted downward and outward, freeing it laterally and from the trachea. The middle thyroid vessels were ligated and cut. The inferior thyroid vessels were ligated close to the gland and cut. A row of hemostats was placed on the vessels on the lateral side of the right lobe, marking out the amount of gland to be left on that side following amputation of that lobe. The isthmus was divided. The right lobe was amputated from within outward leaving a small shell of gland approximately 3x1x0.5 cm. on the posterior capsule.

Occasionally during the past two years, the vocal cords have been examined by direct laryngoscopy after the removal of one lobe and at the conclusion of the operation. The left lobe was then excised in a manner similar to that described for the right. The wound was closed without drainage except in large substernal goiters. During the operation the patients received 1,000-1,500 cc. of normal salt solution by hypodermoclysis.

Postoperative Care.—The proper care of the patients following thyroidectomy was considered most important. After their return to the ward they were temporarily placed in a semi-Fowler position. Frequent change of position was stressed. For the first 24-48 hours they received 300 cc. of tap water by rectum every four hours. Thirty grains of sodium bromide was usually given in the first and third rectal instillations. Lugol's solution, minims ten, was administered three times daily by mouth or in the rectal tap

water. Morphine sulphate 0.01-0.015 Gm. was administered hypodermically every four hours as needed for pain or restlessness. In the severely toxic patients oxygen was administered during the first 24-48 hours. Usually the patients began to take hot water by mouth 12 hours after operation and a liquid diet on the second day. All stitches were removed on the second postoperative day. The patients were usually up on the fifth or sixth day and left the hospital on the seventh. A postoperative laryngeal examination was always made.

The toxic cases were kept on Lugol's solution, minims five, three times daily for four months postoperatively to prevent too rapid regeneration of the remaining thyroid. The patients were followed in the Thyroid Clinic every month for three months, then every two months for one year and then every six months thereafter. Check-up determinations of basal metabolisms were made one month postoperatively and when indicated thereafter.

POSTOPERATIVE COMPLICATIONS

TABLE II

SUMMARY OF POSTOPERATIVE COMPLICATIONS

(1) Wound		17
(a) Infections	2	
(b) Hematomata	6	
(c) Serum	9	
(2) Tetany		8
(3) Pulmonary		6
(4) Toxic psychoses		2
(5) Thyroid crises		6
(6) Burns (prep. sol.)		2
(7) Recurrences (1 goiter only)		10
(8) Vocal cord palsies		31
(9) Deaths		5

(1) *Wound Complications.*—There were 17 wound complications. These varied from small serum collections to infections:

(a) Two wounds were infected, one in which catgut technic was utilized and the wound drained; and the other in a patient closed with silk.

(b) Hematomata developed in six cases. The hematomata were aspirated or evacuated; and the time of wound healing was not prolonged in most cases. Postoperative hemorrhage, in two cases, was sufficiently severe to require the return of the patients to the operating room for religation of bleeding points.

(c) In nine cases, all closed with catgut, there were serum collections requiring aspiration or drainage.

(2) *Tetany.*—Eight patients had tetany postoperatively. Six of the cases were mild and required small amounts of calcium by mouth for from one to three weeks. One of the cases of tetany was moderately severe, requiring calcium and parathormone. She had a positive Chvostek for six months. One patient had severe postoperative tetany. Her blood calcium fell to 6.2 mg. per cent; and the blood phosphorus rose to 5 mg. per cent. She re-

quired parathormone and intravenous calcium chloride. Later, it was possible to control the tetany with viosterol and calcium by mouth. Two years after the thyroidectomy she still needs four drops of viosterol and two tablespoonfuls of calcium daily.

(3) *Pulmonary Complications.*—Six patients had postoperative pulmonary complications. Two patients had atelectasis. In both cases the atelectasis occurred on the second postoperative day and entirely cleared up in two days. Four patients had bronchopneumonia. One of these patients died two days after operation.

(4) *Toxic Psychoses.*—Two patients exhibited toxic psychoses after operation. Neither had had mental symptoms prior to operation. Both developed delusions of persecution which entirely cleared up within three weeks after the operation.

(5) *Thyroid Crises.*—Six patients ran stormy postoperative courses, characterized by fever, rapid pulse and rapid respiration. One of the patients was operated upon in two stages, the first being a lobectomy and polar ligation. She ran a stormy course after each stage. Each of these patients had high basal rates, and two of them had had previous attacks of auricular fibrillation.

(6) *Burns.*—Two patients received mild burns upon the upper back from puddling of the solutions used for skin preparation. Solutions used in these cases were ether, alcohol and 4 per cent tincture of iodine.

(7) *Recurrences.*—Nine patients in this series had a recurrence of their toxic symptoms. One patient, operated upon for a nontoxic adenoma, later developed another adenoma. Five of the patients with recurrent toxic symptoms were reoperated upon with complete relief of symptoms. The patient with a recurrence of nontoxic adenoma declined another operation. Three patients with mild toxic symptoms were treated with roentgenotherapy with complete relief of symptoms. One patient, who is mildly toxic, is being carried along on small doses of iodine.

(8) *Vocal Cord Palsies.*—Routine postoperative examination of the vocal cords showed a paralysis of one cord in 30 cases and a temporary paralysis of both cords in one case. No patients have lost their voices nor have they had respiratory difficulties. The patient with the temporary bilateral cord palsy had tuberculosis of the thyroid. It was considered to be carcinoma at the operation, and a radical excision was performed. The function of both cords returned in six months. In at least seven of the unilateral cord palsies the function of the cord returned after four to six months.

In two of the cases thyroidectomy was performed for carcinoma and the recurrent laryngeal nerve was deliberately sacrificed on one side. Five of the palsies occurred in cases of recurrent goiter and the operation was more difficult because of the scarring.

(9) *Fatalities.*—Five patients died during or after operation, mortality rate for all cases of 1.46 per cent. Three of the deaths occurred in patients with hyperplastic toxic goiter and two in patients with toxic adenomata.

For detailed analysis of the postoperative deaths, see the summaries at the conclusion of the paper. In the period between 1932–1939, there were 192 consecutive thyroidectomies without a death.

End-Results.—Tables III and IV summarize the end-results of all cases followed in this series.

TABLE III

END-RESULTS OF THYROIDECTOMY DURING A 13-YEAR PERIOD

	Sex	A*	A-Hypo*	B*	R*	Deaths H*	Deaths O*	No F-U*	Total
Diffuse toxic goiter	F	73	18	9	7	2	1	6	116
	M	28	5	..	1	1	2	4	41
Adenoma:									
Nontoxic	F	49	4	5	..	..	..	8	66
	M	8	..	..	1†	..	1	2	12
Toxic	F	41	9	3	1	1	1	13	69
	M	4	..	..	..	1	..	1	6
Colloid	F	6	3	1	..	..	..	5	15
Chronic thyroid	F	4	2	1	..	..	..	..	7
Tuberculosis	M	..	1	..	..	..	..	..	1
Neoplastic:									
Benign	F	1	..	..	..	..	..	..	1
Carcinoma	F	..	..	..	..	..	3	..	3
	M	..	..	..	..	..	3	..	3
Lingual thyroid	F	..	1	..	..	..	..	..	1
Totals		214	43	19	10	5	11	39	341

* Key: (A)—Improved. In good health and able to do usual work.
(A-Hypo)—Improved. In good health but taking thyroid extract.
(B)—Slightly improved. No recurrence of hyperthyroidism but still complaining of symptoms noted before operation.
(R)—Recurrence or continuation of hyperthyroidism.
Deaths—(H)—In hospital.
(O)—Sometime after leaving hospital of conditions other than those due to hyperthyroidism.
No (F-U)—No follow-up. Patients not traced or for less than six months.
†—Goiter only.

TABLE IV

Total cases	341
Total cases followed	302
Total toxic cases	232
Recurrences	9
Recurrence rate	3.88%
Total operative mortality	1.46%
Complete relief of symptoms	85%
Partial relief of symptoms	6%
Total cases improved	91%

CONCLUSIONS

(1) Of 341 patients operated upon for goiter during a 13-year period, 257 are known to be improved and in good health. Nineteen are improved but still having symptoms, without hyperthyroidism. Thirty-nine patients could not be followed for a sufficient length of time to be of value in a statistical study.

(2) There were nine recurrences in 232 patients with hyperthyroidism, a recurrence rate of 3.88 per cent. The operative mortality for the entire

group was 1.46 per cent. The operative mortality in the toxic cases was 2.11 per cent.

(3) The most satisfactory results were obtained in those patients in whom a temporary hypothyroidism was obtained. A hypothyroid state is definitely desirable in patients with coronary heart disease.

(4) Paralysis of the recurrent laryngeal nerve can only be determined by routine postoperative laryngeal examinations. A clear voice is no true indication of the normal function of vocal cords. The incidence of paralysis of one cord in this series is high, as disclosed by routine laryngeal examination. Only a few were temporarily inconvenienced by hoarseness and none permanently.

(5) The postoperative administration of iodine is important in preventing excessive thyroid regeneration and recurrence of toxic symptoms.

(6) The operative treatment of hyperthyroidism continues to be the method of choice because of the rapidity with which the results are accomplished; the low operative mortality; and the low incidence of recurrence.

IODINE METABOLISM IN THYROID DISEASE

CLINICAL AND EXPERIMENTAL OBSERVATIONS

J. William Hinton, M.D., Edwin B. Eckerson, M.D., and Maurice Bruger, M.D.

New York, N. Y.

FROM THE COMBINED MEDICAL AND SURGICAL THYROID CLINIC, AND THE MEDICAL RESEARCH LABORATORY, NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL, COLUMBIA UNIVERSITY, NEW YORK, N. Y.

The surgical management of classic cases of hyperthyroidism has given satisfactory end-results during the past two decades. Hyperthyroidism, nevertheless, has often been confused with hypermetabolism. Not infrequently, patients are seen manifesting none of the cardinal signs and symptoms of hyperthyroidism, but in whom an elevated basal metabolic rate has been uncovered. A diagnosis of hyperthyroidism is erroneously made and surgery advised. The end-results from surgical management of this type of case have been unsatisfactory.

In contrast to patients who manifest hypermetabolism alone, are others who present symptoms suggestive of hyperthyroidism, although these may be difficult to evaluate, and in whom the basal metabolic rate is moderately elevated, usually to the extent of 15 to 30 per cent above the average normal. These patients are generally labeled "borderline" hyperthyroidism. From our experience during the past few years, an accurate diagnosis in 20 per cent of these patients has been impossible, although extensive laboratory tests including blood iodine, plasma cholesterol and galactose tolerance tests were carried out for assistance.

In this presentation, our clinical impressions on the value of blood iodine determinations in thyroid disease will be discussed. Experimental studies on the blood and thyroid gland iodine of guinea-pigs receiving equivalent amounts of iodine in various inorganic and organic combinations and thyrotropic factor of the anterior pituitary will also be summarized.

Iodine plays a significant rôle in all forms of thyroid disease. For this reason, some of the recent findings in iodine metabolism for the body at large, as well as for the thyroid gland, will be reviewed.

The human body as a whole contains approximately 40 mg. of iodine distributed as follows: Muscles, 50 per cent; thyroid gland, 20 per cent; skin, 10 per cent; skeletal system, 7 per cent; and the remaining 13 per cent in other endocrine glands, organs and central nervous system (Sturm and Buchholz[1]).

The thyroid gland is principally concerned with the metabolism of iodine, and this is apparent when one considers that a gland which weighs only 20 Gm. contains one-fifth of all the iodine in the body. The adult human contains less iodine than that present in 7 M. of Lugol's solution, since 1 M. of this solution contains 6 mg. of iodine (Means[2]). The amount of iodine necessary to keep a normal person in balance is between 100 and 200 micrograms in 24 hours (a microgram is one-thousandth part of a milligram). In

other words, one drop of Lugol's solution every 30 days is sufficient for normal iodine balance. According to Salter,[3] the entire blood of a normal human contains only one-half milligram of thyroxine.

The normal physiology of the thyroid gland is a delicately balanced mechanism. The cells of the acini have apparently a dual capacity in a normal state of health. They secrete iodine into the colloid of the acini where it is stored as thyroglobulin and later the iodine is removed from the colloid and discharged into the blood stream by the same cells (Carlson and Woelfel[4]). The recent work on radioactive iodine by Hamilton, Soley and Eichorn,[5] demonstrates that the colloid in the acini of a normal gland has the iodine evenly distributed throughout, whereas the colloid of the hyperplastic gland, without previous iodine medication, will show very little if any iodine. They show, further, that in colloid goiters, the greatest concentration of iodine is in the acinal cells and in the colloid at the periphery of the distended acini; the central portions of the colloid have little demonstrable iodins. In a normal acinus the colloid is alkaline in reaction, whereas in a long-standing distended acinus, the central portion of the colloid becomes acid and under these latter circumstances the colloid is not reabsorbable or utilizable by the cells for normal distribution (Hewer[6]). This does not prove that the distended acini of a colloid goiter contain a physiologically inactive product. By means of rapid freezing, Tatum,[7] and van Dyke[8] were able to separate the colloid from the cell mass, and demonstrated that 85 per cent of the iodine in the thyroid gland was in the colloid. Using the method of Tatum and van Dyke, Williamson, Pearse and Cunnington[9] isolated two types of colloid from the same gland. From that portion of the gland called inactive by histologic study, the colloid contained not only an abundance of iodine but was physiologically active by the tadpole test. The colloid from the active portion of the gland contained very little iodine and was physiologically inactive.

Marine and Lenhart[10] emphasized the part played by iodine deficiency in the production of colloid goiter. They believed that: First, hyperplasia of the acinal cells occurred; and that this was followed by dilatation of the acini, with atrophy and exhaustion of the cells. Marine and Lenhart found the normal thyroid gland, expressed in dry weight, contained from 0.1 per cent to 0.55 per cent iodine. Values less than 0.10 per cent represented iodine deficiency. In the New York City area, Gutman, Benedict, Baxter and Palmer[11] found the normal thyroid gland contained on the average 0.186 per cent iodine. In the same locality, our[12] values averaged 0.130 per cent iodine.

It is important to consider the chemical nature of iodine as it exists in the thyroid gland. Salter[13] found that not more than 10 per cent of the total iodine in the thyroid gland was inorganic in nature; 90 per cent or more was in organic combination approximately two-thirds of which was in the form of diiodotyrosine and one-third thyroxine. In 1927, Harington and Barger[14] showed that thyroxine was a derivative of tyrosine. Obviously, the first requirement necessary for the production of adequate quantities of thyroid hormone is a complete hydrolysis of ingested protein into amino-acids. Suf-

ficient amounts of tyrosine thus released must then be supplied to the thyroid gland for combination with iodine. Three iodo-amino-acids are recognized—monoiodotyrosine containing 39.1 per cent iodine; diiodotyrosine with 58.7 per cent iodine; and thyroxine containing 65.4 per cent iodine. Unlike thyroxine, the first two of these are physiologically inactive. Means, Lerman and Salter[15] demonstrated a synergistic action between thyroxine and diiodotyrosine since thyroglobulin which contains both of these iodo-amino-acids was more active in the treatment of myxedema than an equivalent amount of thyroxine given alone. Abelin[16] prepared a physiologically active product from the alkaline hydrolysis of iodinated casein; the administration of this material to patients with myxedema relieved their symptoms. Ludwig and Mutzenbecher[17] isolated diiodotyrosine and thyroxine from iodinated casein in the same ratio as they exist in the thyroid gland. Salter and Lerman[18] were able to iodinate serum albumin, and thus prepare a physiologically active substance without hydrolysis, which was also effective in relieving myxedema. These significant findings indicate that the thyroid gland may play a very small part in the manufacture of physiologically active iodine compounds as they exist in the human boly.

This brings us to a consideration of disorders of the thyroid gland in localities where iodine deficiency does not exist. Can thyroid disease under these circumstances be considered as due to the lack of iodine in the body or perhaps due to a deficiency of tyrosine which supplies the organic radical? Protein metabolism, with failure to supply adequate amounts of tyrosine to the thyroid gland, may be a potent factor in the production of thyroid disease. Morton, Weeks, and one of us[19] have shown that colloid goiters can be produced in dogs by the ligation of the pancreatic ducts. Under these conditions, interference with tryptic digestion might result in the incomplete hydrolysis of ingested protein with consequent failure to supply adequate quantities of tyrosine to the thryoid gland.

Experimental Studies.—It is generally known that the colloid type of goiter does not respond satisfactorily to treatment with inorganic iodine. For this reason, primarily, the following experiments were carried out. Potassium iodide, sodium iodide, diiodotyrosine, thyroglobulin and thyroxine were administered to guinea-pigs in doses of one microgram of iodine per gram of body weight, every 72 hours for three doses. The animals were autopsied 72 hours after the last dose of iodine. Thyrotropic factor of the anterior pituitary* (which contains no iodine) in doses of 1 cc. every 72 hours, for three doses, was also given to another group of guinea-pigs. All injections were intraperitoneal. Seven to 8 cc. of blood were removed from the heart just before the animals were sacrificed and the total blood iodine determined. The right lobe of the thyroid gland was analyzed for iodine content and the left lobe taken for histologic study. The iodine findings in both blood and thyroid glands are summarized in Table I.

* This material was supplied through the courtesy of Ayerst, McKenna and Harrison of Montreal, Canada, and Rouses Point, New York.

TABLE I

THE EFFECT OF THE INJECTION OF EQUIVALENT AMOUNTS OF IODINE IN INORGANIC AND ORGANIC COMBINATION AND OF THYROTROPIC FACTOR OF THE ANTERIOR PITUITARY ON THE IODINE CONTENT OF THE THYROID GLAND AND BLOOD OF GUINEA-PIGS

	Thyroid Gland			Whole Blood		
Group	No. of Animals	Mean Iodine Content*	Standard Deviation	No. of Animals	Mean Iodine Content γ/100 cc.	Standard Deviation
Control	11	5.25	1.36	5	7.3	1.63
Potassium iodide	15	8.29	3.15	12	16.0	3.23
Sodium iodide	11	6.59	2.35	6	12.0	3.59
Thyroxine	14	8.15	1.72	12	20.9	3.36
Diiodotyrosine	12	7.71	1.94	9	9.1	3.25
Thyroglobulin	8	6.70	1.27	8	20.7	8.05
Thyrotropic factor of anterior pituitary	13	4.45	1.42	11	7.2	2.93

* These values represent the micrograms of iodine in the thyroid gland, per 100 grams of body weight, calculated from the following formula:

$$\gamma \text{ thyroid iodine/100 Gm., body weight} = \frac{\text{Iodine content of right lobe (microgm.)} \times 2 \times 100}{\text{Body weight (grams)}}$$

In 11 guinea-pigs used as controls, the mean iodine content of the thyroid gland expressed as micrograms per 100 grams of body weight was 5.25 ± 1.36. In five of these, the mean whole blood iodine was 7.3 ± 1.63 micrograms per 100 cc. The administration of iodine in organic or inorganic combinations, as would be expected, elevated the mean thyroid and blood iodine. Although equivalent amounts of iodine were used throughout, Table I shows that diiodotyrosine and thyroxine resulted in a higher average blood iodine than that produced by iodine in inorganic combination; the increase in the iodine contents of the thyroid glands following organic or inorganic iodine were not dissimilar. The administration of thyrotropic factor of the anterior pituitary was followed by a decrease in the iodine content of the thyroid gland as has been shown previously by Closs, Loeb and MacKay,[20] and others.[21, 22] The increase in blood iodine following the injection of thyrotropic factor in guinea-pigs reported by Closs and his coworkers was not observed in our animals but this may have been due to the smaller dose of hormone used in the present experiments.

Histologic studies revealed that potassium iodide, sodium iodide and diiodotyrosine in the doses administered failed to produce any noteworthy changes in the thyroid glands of the guinea-pigs. The animals receiving thyroxine and thyroglobulin gave evidence of increased cellular activity perhaps a shade more so in those injected with thryoglobulin. The guinea-pigs receiving thyrotropic factor of the anterior pituitary showed by far the greatest degree of cellular activity as indicated by hypertrophy and hyperplasia of the acinal cells. Figures 1, 2 and 3 are photomicrographs of sections of the thyroid gland of a control guinea-pig, of one injected with thyroglobulin and one receiving thyrotropic hormone, respectively, which illustrate the differences noted above.

Since Williamson, Pearse and Cunnington[9] have shown that the so-called

"inactive" colloid is both physiologically active by the tadpole test, and contains appreciable quantities of iodine, it appears that the ideal medication for colloid goiter would be the administration of thyrotropic hormone since the resultant stimulation of cellular activity would favor resorption of the colloid by the acinal cells and reduction of the iodine content of the thyroid gland.

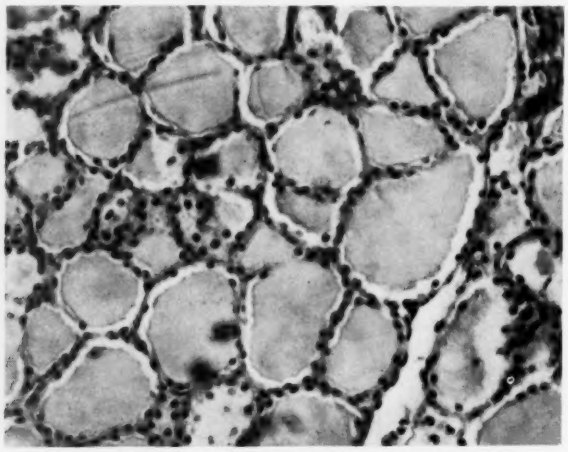


FIG. 1.—Photomicrograph of a section of a thyroid gland of a control guinea-pig. (×375)

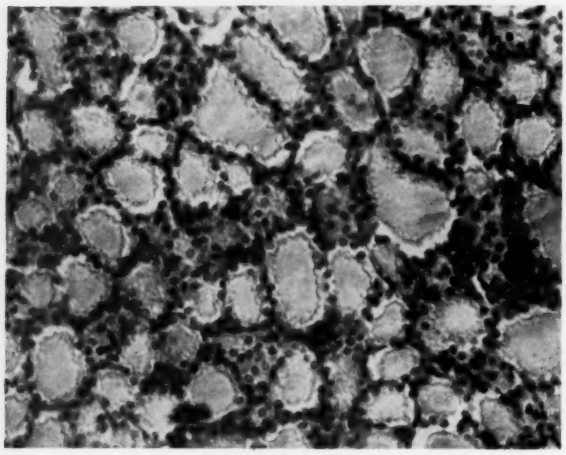


FIG. 2.—Photomicrograph of a section of a thyroid gland of a guinea-pig receiving thyroglobulin. (×375)

Theoretically, thyroglobulin and thyroxine would be less preferable, since cellular activity is not profoundly influenced as by thyrotropic hormone and, moreover, the iodine content of the thyroid gland would increase. Thyrotropic factor of the anterior pituitary is now being used for the treatment of colloid goiter in our clinic; as yet, our clinical trials have not been extensive or prolonged enough to report on its efficacy.

Studies on Blood Iodine in Thyroid Disease.—Up to the present time, 303 determinations on the total iodine content of the blood have been carried

out on 236 patients, who had, or were suspected of having thyroid disease. As far as could be determined, none of the patients had been taking iodine-containing compounds within one month of the blood studies. The findings are summarized in Table II.

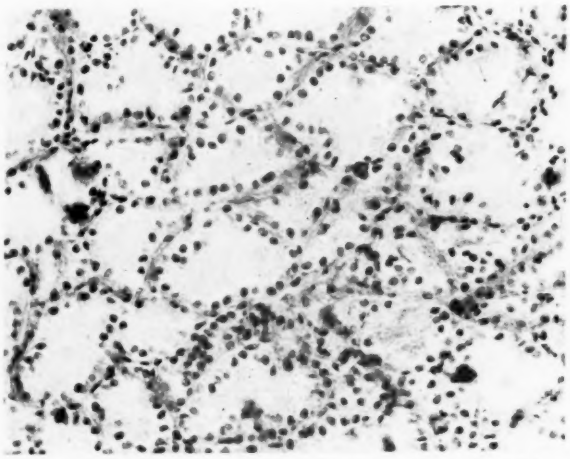


FIG. 3.—Photomicrograph of a section of a thyroid gland of a guinea-pig receiving thyrotropic factor of the anterior pituitary. (×375)

TABLE II

CORRELATION OF BLOOD IODINE WITH TYPE OF THYROID DISEASE

303 Blood Iodine Determinations in 236 Patients

		Whole Blood Iodine (γ per 100 cc.)							
		2 to 3		3 to 9 (normal range)		9 to 30		Over 30	
Diagnosis	No. of Cases	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
No thyroid disease	65	1	1.5	46	70.8	18	27.7	0	0
Exophthalmic goiter	66	0	0	14	21.2	50	75.8	2	3.0
Persistent exophthalmic goiter	8	0	0	6	75.0	2	25.0	0	0
Recurrent exophthalmic goiter	8	0	0	5	62.5	3	37.5	0	0
"Borderline" hyperthyroidism	8	0	0	4	50.0	4	50.0	0	0
Nontoxic nodular goiter	39	1	2.6	30	76.9	8	20.5	0	0
Toxic nodular goiter	19	0	0	10	52.6	9	47.4	0	0
Colloid goiter	11	0	0	10	90.9	1	9.1	0	0
Hypothyroidism or myxedema	12	2	16.7	10	83.3	0	0	0	0

We[23] have shown that in normal subjects, carefully selected so as to exclude, as far as possible, obvious exposure to iodine, the total blood iodine varied between 3.1 and 8.4 micrograms per 100 cc. with a mean of 5.9 ± 1.3. In 65 patients, in whom the presence of thyroid disease was eliminated (these include patients with anxiety neuroses, vasomotor instability, *etc.*) 18, or 27.7 per cent, had elevated blood iodine (between 9 and 30 micograms per 100 cc.). The remainder, with one exception, showed normal values. Experience in blood iodine studies during the past three and one-half years, had taught us that such high values in patients with nonthyroid disease represent

undue exposure to iodine. It must not be overlooked that many drugs, particularly bromides, are contaminated with iodine; moreover, iodine is commonly used in many households for skin antisepsis. The use of iodine compounds in radiographic work is universal and a frequent unsuspected source of excessive iodine intake.[24] The fact that approximately 25 per cent of patients with nonthyroid disease show an increased concentration of total iodine in the blood does not nullify the value of such determinations in patients with thyroid disease. It merely serves to emphasize that caution should be exercised in interpreting the results of total blood iodine. Limiting blood iodine studies to the organic fraction (presumably, the circulating thyroid hormone) will probably prove to be the preferable determination. Observations on the organic iodine fraction of the blood in patients with thyroid disorders are now being carried out in this clinic, the results of which will be the subject of a later communication.

In 66 patients with exophthalmic goiter, 52, or 78.8 per cent, had an elevated blood iodine. In 32 of these, the duration of the disease was one year or less and 27, or 84.4 per cent, had an elevated blood iodine. In 34 patients, the duration of the exophthalmic goiter was more than one year, and in this group 26, or 76.5 per cent, showed an increased blood iodine. These findings are at variance with those of Perkin and Cattell,[25] who maintained that in long-standing cases of exophthalmic goiter, the blood iodine falls within normal limits.

The incidence of an increased blood iodine in toxic nodular goiter and in the so-called "borderline" exophthalmic goiter was approximately the same, *i.e.*, about 50 per cent. In 11 patients with colloid goiter, ten, or 90.9 per cent, showed a normal blood iodine. In 12 patients with hypothyroidism or myxedema, the blood iodine was normal in ten, or 83.3 per cent, and definitely below the normal range in two, or 16.7 per cent.

In 16 patients with persistent or recurrent exophthalmic goiter, the incidence of an elevated blood iodine was no greater than that observed in nonthyroid patients, a fact which strongly suggests that the diagnosis of hyperthyroidism, which led to surgery in these patients, may have been erroneous and that the decreased iodine content of the blood is not indicative of exhaustion of the thyroid gland. Our clinical experience alone, without the aid of blood iodine determinations, has helped to formulate this opinion.

CONCLUSIONS

(1) Subtotal thyroidectomy in patients with classic hyperthyroidism has given satisfactory end-results for the past two decades.

(2) The advent of the routine use of basal metabolic studies in patients suspected of thyroid disease has led to the confusion between hypermetabolism and hyperthyroidism. In patients manifesting an increased basal metabolism but without clinical signs of hyperthyroidism, subtotal thyroidectomy has been followed by poor end-results.

(3) The blood iodine, thyroid gland iodine, and histology of the thyroid

gland were studied in guinea-pigs following the administration of equivalent amounts of iodine in the form of potassium iodide, sodium iodide, diiodotyrosine, thyroglobulin and thyroxine. Potassium iodide, sodium iodide and diiodotyrosine elevated both the blood and thyroid gland iodine without altering the histologic picture of the thyroid gland. Thyroglobulin and thyroxine also increased the blood and thyroid gland iodine but this was associated with evidence of increased activity of the acinal cells.

(4) The administration of thyrotropic factor of the anterior pituitary (which contained no iodine) to guinea-pigs, resulted in a decrease in the thyroid gland iodine without any changes in the blood iodine. Marked stimulation of cellular activity, and diminution of the colloid content of the acini were observed following the injection of thyrotropic hormone.

(5) Approximately 25 per cent of all patients with nonthyroid disorders, though clinically suspected of having thyoid disease, had an elevated blood iodine. It is believed that a high blood iodine in such patients represents unsuspected exposure to iodine.

(6) Approximately 80 per cent of patients with exophthalmic goiter and 50 per cent with toxic nodular goiter showed an elevated blood iodine.

(7) Contrary to findings of other observers, the level of blood iodine in patients with exophthalmic goiter bore no relation to the duration of the disease.

(8) In persistent or recurrent exophthalmic goiter, the incidence of an elevated blood iodine was no greater than in patients with nonthyroid disease. Clinical experience, in addition to blood iodine studies, has helped to formulate the opinion that in many patients with persistent or recurrent exophthalmic goiter, the diagnosis of hyperthyroidism, which led to surgery, was probably erroneous and that the decreased iodine content of the blood was not indicative of the exhaustion of the thyroid gland.

Samuel Member, B. S., and Julius Wiland, B. S., rendered valuable technical assistance.

REFERENCES

[1] Sturm, A., and Buchholz, B.: Beiträge zur Kenntnis des Jodstoffwechsels. IV. Mitt. Jodverteilung im menschlichen und tierischen Organismus in ihrer Beziehung zur Schilddrüse. Deutsch. Arch. f. klin. Med., **161**, *227*, 1928.

[2] Means, J. H.: The Thyroid and Its Diseases. Philadelphia, J. B. Lippincott Co., 1937, p. 350.

[3] Salter, W. T.: The Endocrine Function of Iodine, The Harvard University Press, Cambridge, Mass., 1940, page 76.

[4] Carlson, A. J., and Woelfel, A.: On the Internal Secretion of the Thyroid Gland, Am. Jour. Physiol., **26**, *32*, 1910.

[5] Hamilton, J. G., Soley, M. H., and Eichorn, K. B.: Deposition of Radio-active Iodine in Human Thyroid Tissue. Univ. Calif. Pub. in Pharmacol., **1**, 339, 1940.

[6] Hewer, E. E.: The Activity of the Thyroid Gland in Relation to the Staining Reactions of the Colloid. Jour. Path. and Bact., **30**, 621, 1927.

[7] Tatum, A. L.: A Study of the Distribution of Iodine between Cells and Colloid in the Thyroid Gland. I. Methods and Results of Study of Beef, Sheep and Pig Thyroid Glands. Jour. Biol. Chem., **42**, 47, 1920.

[8] van Dyke, H. B.: A Study of the Distribution of Iodine between Cells and Colloid in the Thyroid Gland. II. Results of Study of Dog and Human Glands. Jour. Biol. Chem., **45,** 325, 1920–21.

[9] Williamson, G. S., Pearse, I. H., and Cunnington, H. M.: The Two Products of Thyroid Activity. Jour. Path. and Bact., **31,** 255, 1928.

[10] Marine, D., and Lenhart, C. H.: Effects of the Administration or the Withholding of Iodine Containing Compounds in Normal, Colloid or Actively Hyperplastic (Parenchymatous) Thyroids of Dogs. Arch. Int. Med., **4,** 253, 1909.

[11] Gutman, A. B., Benedict, E. N., Baxter, B., and Palmer, W. W.: The Effect of Administration of Iodine on the Total Iodine, Inorganic Iodine, and Thyroxine Content of the Pathologic Thyroid Gland. Tr. Am. Assn. Study Goiter, 1932, p. 31.

[12] Hinton, J. W., Lough, W. G., and Bruger, M.: The Iodine Content of the Normal and Pathologic Thyroid Gland. Unpublished results.

[13] Salter, W. T., *loc. cit.* Reference 3, p. 24.

[14] Harington, C. R., and Barger, G.: Chemistry of Thyroxine. III. Constitution and Synthesis of Thyroxine. Biochem. Jour., **21,** 169, 1927.

[15] Means, J. H., Lerman, J., and Salter, W. T.: The Rôle of Thyroxine Iodine and Total Organic Iodine in the Calorigenic Action of Whole Thyroid Gland. Jour. Clin. Invest., **12,** 683, 1933.

[16] Abelin, I.: Über die extrathyreoidale Entstehung thyroxinartig wirkender Jodverbindungen. Klin. Wchnschr., **13,** 940, 1934.

[17] Ludwig, W., and v. Mutzenbecher, P.: Über die Entstehung von Thyroxin durch Jodierung von Eiweiss. Ztschr. f. physiol. Chem., **244,** iv, 1936.

[18] Salter, W. T., and Lerman, J.: Iodinated Protein in Human Athyreosis. Tr. A. Am. Phys., **53,** 202, 1938.

[19] Hinton, J. W., Morton, P. C., and Weeks, C.: Experimental and Clinical Studies of the Relationship of Thyroid Disease and Pancreatic Function. Annals of Surgery, **99,** 126, 1934.

[20] Closs, K., Loeb, L., and MacKay, E. M.: The Effect of an Acid Extract of the Anterior Pituitary on the Iodine Concentration of the Blood and Thyroid Gland. Jour. Biol. Chem., **96,** 585, 1932.

[21] Schockaert, J. A., and Foster, G. L.: Influence of Anterior Pituitary Substance on the Total Iodine Content of the Thyroid Gland in the Young Duck. Jour. Biol. Chem., **95,** 89, 1932.

[22] Loeser, A., and Thompson, K. W.: Hypophysenvorderlappen, Jod und Schilddrüse. Der Mechanismus der Schilddrüsenwirkung des Jods. Endokrinologie, **14,** 144, 1934.

[23] Bruger, M., Hinton, J. W., and Lough, W. G.: Studies on Iodine Metabolism. I. The Iodine Content of the Blood, Urine and Saliva of Normal Subjects. Unpublished Results.

[24] Greene, C. H., and Bruger, M.: The Iodine Content of the Blood in Diseases of the Liver and Biliary Tract: Clinical and Experimental Studies. Jour. Clin. Invest. (Proc.), **18,** 481, 1939.

[25] Perkin, H. J., and Cattell, R. B.: Blood Iodine Levels Related to the Recurrence of Hyperthyroidism. Surg. Gynec., and Obstet., **68,** 744, 1939.

Read before the New York Surgical Society, April 9, 1941.

CARDIOSPASM

CARL EGGERS, M.D.
NEW YORK, N. Y.

CARDIOSPASM is the designation most commonly applied to a condition which other authors have called diffuse dilatation of the esophagus, idiopathic dilatation, mega-esophagus, achalasia of the cardia, or phrenospasm. These numerous designations suggest that the etiology and pathology are not clearly understood. The name cardiospasm implies that we are dealing with a true spasm at the cardia. Diffuse dilatation stresses the enlargement of the organ. Idiopathic dilatation calls attention to the dilated, relaxed condition of the walls of the esophagus of unknown etiology as the outstanding condition. Mega-esophagus simply means a large esophagus; while achalasia implies the inability of the cardia to open normally. Phrenospasm or phreno-esophagospasm emphasizes the pinch-cock action of the diaphragm as an etiologic factor.

Plummer[1] feels that the adoption of the term "cardiospasm" is premature and confusing, as the part that spasm of the cardia plays in the production of diffuse dilatation is by no means established. Moreover, there are many cases, probably not directly related, that have spasm at the cardiac orifice without dilatation of the esophagus.

Whatever designation is used, the diagnosis of the condition under consideration rests on finding a diffuse dilatation of the esophagus with obstruction at its lower end during the life of the patient, but without anatomic stenosis demonstrable either at operation or at postmortem examination. All other lesions have to be excluded from the discussion.

Cardiospasm is second in frequency to carcinoma in producing symptoms of esophageal obstruction. It may affect people of all ages, including infants and children. The outstanding symptoms are pain, dysphagia and regurgitation. The onset may be sudden and intermittent at first but is usually gradual with dysphagia as the only symptom. In other cases pain predominates. Later there is regurgitation of food, a sense of fullness or pressure associated with substernal or epigastric pain and possibly anemia and loss of weight. The pain may be increased by taking food or it may be independent of deglutition. Often it is very severe and radiates to the back. As the esophagus becomes more and more dilated, shortness of breath develops on exertion or on lying down. The patient may have difficulty resting at night owing to the pressure of the overloaded esophagus and because the liquid contents leak out and spill into the larynx, bringing on paroxysms of coughing. Aspiration may result and lead to pulmonary suppuration. Frequently there is loss of weight, which may assume alarming proportions.

Physical examination is negative, except perhaps for loss of weight and possible pulmonary complications. The patients may be rather nervous and apprehensive and they frequently are of the opinion that excitement, worry or fatigue are responsible for the aggravation of symptoms. Plummer[1] and Vinson,[2] however, who have had extensive experience with this condition, state

positively that it is not a neurosis. It is possible that the psychogenic factors are secondary to the underlying condition.

Roentgenologic examination with a contrast medium shows dilatation of the esophagus ending usually at the level of the diaphragm but sometimes at a

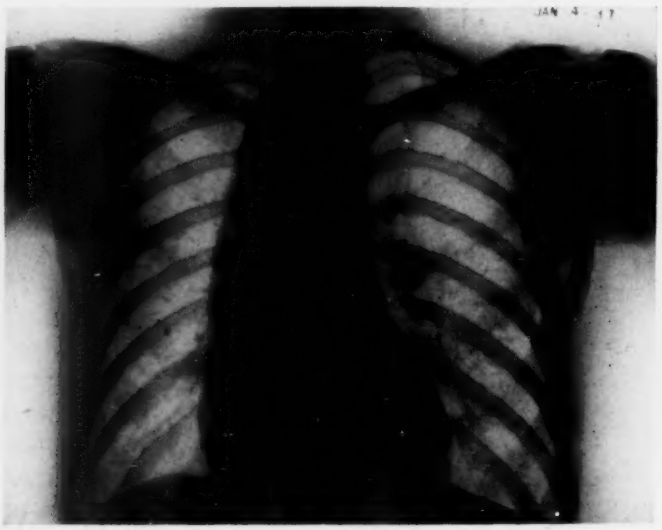


FIG. 1.—(A) Straight shadow of enormously distended esophagus. Condition present since childhood.

somewhat higher level, in a smooth, tapering constriction. This constant observation has given rise to the belief that there is a sphincter in the wall of the esophagus beginning at about the level of the diaphragm or that the diaphragm or its crura act as a pinchcock at this point. Only very rarely has the esophageal dilatation been observed to extend to the anatomic cardia. Peristaltic waves are often observed on fluoroscopic observation and occasionally reverse peristalsis is present.

FIG. 1.—(B) Appearance after partial evacuation of retained contents, consisting of a frothy food mixture.

In patients in whom the condition has existed for a long time, preliminary roentgenogram of the chest may show the straight border of a shadow of increased density extending into the lung field to the right of the cardiac and upper mediastinal shadows. If this examination is made in the erect position a fluid

level may be present in the superior mediastinum due to air and retained matter in the dilated esophagus (Fig. 1A). When barium is given to such a patient it is seen to float down in streams through the retained material. Only very little barium enters the stomach (Fig. 1B).

In some cases of long standing cardiospasm the esophagus becomes elongated and sacculated, producing an appearance simulating a diverticulum.

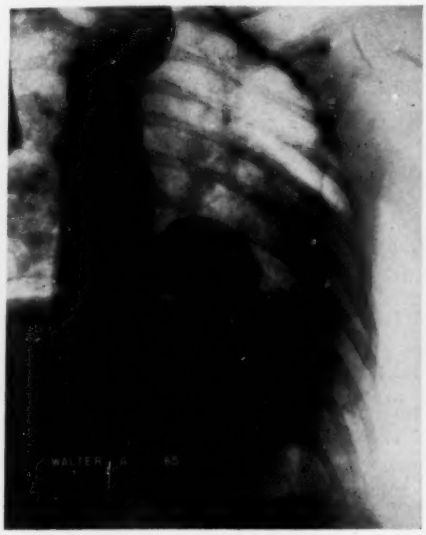


FIG. 2.—Enormous dilatation of esophagus with elongation and sacculation. Peristaltic waves are still present.

FIG. 3.—Cardiospasm with secondary development of diverticula.

Twenty-four-hour retention in the esophagus is not uncommon (Fig. 2). Actual diverticula may also develop as the result of pressure within the esophagus, causing bulging at weak portions of the wall (Fig. 3).

Esophagoscopy is of great value in differential diagnosis and should be carried out whenever there is any question as to the cause of obstruction. The walls of the esophagus usually look pale and flabby. In older cases, with retention, the esophagus is found to be filled with frothy liquid content which has to be evacuated before visualization is possible. In such cases the mucosa is congested and frequently ulcerated and the cardia may be difficult to locate. The passage of an esophageal sound over a previously swallowed silk thread may be more important in diagnosis than an esophagoscopy. It passes into the stomach with no more than the usual slight elastic resistance, whereas in patients with benign stenosis or carcinoma, a definite stricture can be detected.

One of the very interesting observations in connection with cardiospasm is that although marked obstruction exists, which eventually leads to enormous dilatation of the esophagus, no gross anatomic change is observed or can be demonstrated below the dilatation either during operation or at autopsy.

Many suggestions have been made to explain the obstruction. One of the oldest is that we are dealing with a sphincter spasm. This naturally presup-

poses the presence of a sphincter. However, neither at operation or autopsy has such an anatomic sphincter been demonstrated. No thickening similar to the tumor found in hypertrophic pyloric stenosis has been visualized. Knight,[3] however, has recently submitted experimental evidence supporting the theory of spasm as the cause of obstruction. He has demonstrated in cats that the interdiaphragmatic and intra-abdominal portions of the esophagus function as a true intrinsic sphincter, which is relaxed by the vagus nerve and contracts on sympathetic stimulation. The sphincter is capable of functioning independently of surrounding structures and receives its sympathetic supply from the celiac plexus in fibers which follow the course of the left gastric artery and its esophageal branch to the lower end of the esophagus. He was able to show definitely with illustrations, that bilateral vagus section in cats reproduced the roentgenographic, pathologic and clinical picture of achalasia of the cardia. The sphincter failed to relax. If, however, celiac sympathectomy, with a consequent denervation of the sympathetic fibers, was performed at the same time that the vagi were divided, no obstruction resulted at the cardia; the sphincter always relaxed to allow the meal to enter the stomach. He comes to the conclusion that whether the obstruction is caused by failure of the vagus to open the cardia, or by spasm, in either case the integrity of the sympathetic supply is necessary for the obstruction to occur, and, therefore, it can be relieved by sympathectomy. In a recent anatomic study based upon careful dissection of 14 cadavers, Mitchell[4] states that any peripheral operation to produce complete sympathetic denervation of the cardiac orifice of the esophagus would have to be more radical than the one proposed by Knight. The magnitude of an operation to interrupt all possible sympathetic fibers to the lower esophagus might be greater than is justified by the symptoms usually produced by cardiospasm.

In contrast to the theory of spasm of a sphincter at the lower end of the esophagus producing the symptoms of so called cardiospasm, Jackson[5] believes cardiospasm is an erroneous term. He states spasm in these patients is never greater than minimal normal. He holds muscular and tendinous prolongations of the crura, which surround the esophagus, to be responsible for normal closure and opening of the lower end of the esophagus. He calls this the diaphragmatic pinch-cock. According to his theory, it is the failure of this pinch-cock to open in the deglutitory cycle, and not any excessive spasm, that is the chief etiologic factor in many cases of cardiospasm.

That the diaphragm may play a rôle in the function of the esophagus has been suggested by numerous roentgenologists who have observed temporary stoppage of the barium meal at the cardia during deep inspiration. Barsony and Wald[6] examined their patients in a straight lateral position. In some cases of cardiospasm the barium remains arrested at the diaphragmatic hiatus during entire inspiration, even if prolonged. In other cases of cardiospasm some barium enters the abdominal part of the esophagus during the latter part of inspiration and fills the esophagus to the anatomic cardia. Therefore, in some cases, with roentgenograms taken in inspiration, the site of arrest of the barium is the hiatus, in others the cardia. The differentiation of cardia and

hiatus-spasm can often be made only if several films are taken in expiration or various phases of inspiration in straight lateral position. Mosher[7] has made similar observations and ascribes an important rôle to the liver tunnel through which the lower part of the esophagus passes. Hurst[8] also believes that the inability of the cardia to open, which is normally the last stage of the act of deglutition, is responsible for the dysphagia and the secondary dilatation and hypertrophy. He has applied the name "achalasia," which means inability to open, to this dysfunction, and attributes it to pathologic changes in Auerbach's plexus. This plexus is composed of ganglion cells and nerve fibers derived from the vagi, and is situated between the circular and longitudinal muscle coats. At first there is round celled infiltration, which is later replaced by fibrous tissue with complete disappearance of the ganglion cells at the lower end of the esophagus. He states that the primary cause of the change in Auerbach's plexus is unknown, but as the vagi contain the fibers which cause the sphincter to open, their degeneration results in achalasia. Rake[9] has presented histologic evidence of the progressive degeneration of Auerbach's plexus, which is present in at least some cases of cardiospasm.

In the absence of an anatomically demonstrable sphincter, Hurst visualizes a functional sphincter at the cardia, about one inch long, and situated entirely below the diaphragm. This corresponds with the observations of the absence of an anatomic sphincter, but a closed lower end of the esophagus, usually extending from the hiatus of the diaphragm to the cardia proper. If this theory is correct, this entire lower portion should be considered cardia, for the purpose of discussion, because it has a nerve supply the function of which differs from that of the rest of the esophagus.

The closed cardia in a patient with cardiospasm resists a water pressure of eight inches. According to Hurst,[8] it is only when the column rises beyond this level that food is forced through the cardia and enters the stomach.

Heyrovsky[10] states that the vagus not alone supplies the muscles of the esophagus, but also influences the tone of the cardia by contracting or relaxing it. One may, therefore, assume that in addition to atony of the esophagus, one may have not alone absence of normal relaxation of the cardia, but even increase of spasm beyond the normal. Much depends on whether the case is seen early or late in the disease.

A voluminous literature on cardiospasm has accumulated, dealing chiefly with its etiology. Much of it is confusing. The whole question of the etiology of cardiospasm requires further study, for the isolated clinical and experimental observations are still so much at variance, that no definite conclusions can be drawn. However, evidence is accumulating and appears quite conclusive that the condition is due to a neuromuscular dysfunction resulting from pathologic changes in the vagi, and more particularly in Auerbach's plexus. What these changes are due to, has not been determined. They may be of an inflammatory nature or the result of nutritional disturbance or avitaminosis. Recent investigations of cardiospasm have unearthed many facts that support the theory that nutritional and vitamin deficiencies play an important rôle in

the etiology. It may be that all cases of cardiospasm are not due to the same etiologic factor, and, therefore, the inability to explain a particular case on the grounds of a nutritional or vitamin deficiency does not rule it out as an etiologic agent. Cardiospasm is very common in some parts of Brazil, according to Etzel and Vasconcelos. Etzel[11] observed 626 cases in an 18-year period; most of these cases came from rural districts of Brazil where the diet is poor and inadequate, and especially low in Vitamin B_1. The theory that cardiospasm is caused by a defect in the nerve plexuses did not explain the reason for these histologic findings. The changes in Auerbach's plexus may be secondary to the nutritional and vitamin deficiency. That cardiospasm is not due merely to local factors affecting the esophagus is suggested by Etzel's observation of the frequent association of cardiospasm or mega-esophagus with megacolon. Etzel found that most of his Italian patients with mega-esophagus and megacolon came from a district in which pellagra is common.

Cardiospasm has to be differentiated from other lesions producing obstruction at the cardia. Benign stricture and carcinoma may be ruled out by the character and the duration of symptoms, combined with the roentgenologic appearance of the lesion. The passage of a sound will aid. Esophagoscopic examination, perhaps with a biopsy, will determine the diagnosis in doubtful cases. The differential diagnosis between cardiospasm and other functional conditions affecting the lower end of the esophagus may be more difficult. Spasm at the cardia may be secondary to an intra-abdominal lesion or a neurosis. Diffuse spasm of the esophagus, which Vinson considers a definite entity, may simulate cardiospasm and is distinguished from it chiefly by sufficient spasm to prevent passage of a No. 60 F. sound into the stomach. Esophagoscopic examination usually reveals tight contraction of the lower esophagus without a visible lumen. Roentgenologic study shows diffuse contraction of the lower half of the esophagus. Diffuse spasm of the esophagus may be secondary to a lesion of the abdomen. Unless the removal of the intra-abdominal focus held responsible for the spasm relieves the condition, the treatment is the same as that for cardiospasm.

Treatment of Cardiospasm.—Most authors believe that spontaneous recovery never occurs, and, with our present knowledge, that there is no treatment which may be considered curative. Once dilatation and hypertrophy have developed, the condition seems to be permanent. The treatment is intended to relieve symptoms by improving drainage from the esophagus to the stomach. The means to do this varies with the conception of the etiology. If one considers spasm at the cardia to be the responsible factor, forcible stretching or dilation of the sphincter would naturally suggest itself as the treatment of choice. In case one believes in the theory of achalasia, an attempt to rectify or overcome the responsible disturbed nervous mechanism is indicated. After enormous dilatation of the esophagus has taken place, with elongation and sacculation, these secondary factors may be more important than the original achalasia or spasm, and require consideration of treatment from a different angle. Without regard to etiology, however, there may be

another approach to the question of treatment and that is expediency and safety. It hardly seems justified to expose a patient to a serious and technically difficult operation if symptomatic relief may be obtained by a simple procedure.

While clinical and experimental investigations are being pursued, practical experience has shown that dilation of the cardia is followed by symptomatic relief.

The less severe cases usually remain under the care of an internist for a long time. Simple remedies are tried with more or less success. Many patients manage to get along fairly well by restricting their diet to bland liquids and soft food; others feel that solid food passes through more easily. Highly seasoned foods and those containing coarse particles usually have to be avoided. One has to be guided by the idiosyncrasies of the patients. They have to be cautioned to eat slowly, to take a small meal frequently, and to choose warm to cold food. Mild sedatives and antispasmodics may be of value. The simple passage of a stomach tube or bougie often brings temporary relief.

If these measures fail, or the condition becomes worse, more energetic treatment becomes indicated. It may be years before the symptoms become so severe that the patient is referred to an endoscopist or a surgeon. Without a definite understanding of the etiology, it has been found that mechanical forcible stretching of the lower end of the esophagus and cardia brings relief for shorter or longer periods. Many dilators have been designed and are in use. Vinson[2] begins with the passage of a No. 41 F. sound passed over a previously swallowed twisted silk thread, and runs it up to No. 60 F. He states this mechanical dilation gives relief in about 10 per cent of cases, and that almost all of those having recurrences after this treatment, and the ones who are not benefited by it, can be cured by dilating the cardia with the Russel hydrostatic dilator. The risk of stretching the cardia with this expanding dilator after the passage of a No. 60 F. sound is negligible.

Moore[12] starts treatment by passing mercury-filled bougies about once a week, beginning with the No. 28 F. This is done one-half hour after giving the patient 1½ gr. nembutal and anesthetizing the throat with a spray of 2 per cent cocaine. If the patient tolerates the procedure well, he passes the next size, the No. 30 F. Each dilator is left in place about five minutes if possible. As the patients become more accustomed to the procedure, two can be passed each time. When the largest size, the No. 34 F., is reached, he encourages them to swallow the Mosher bag, and pumps it up to four pounds for five minutes. This produces a larger amount of stretching than is possible with the nonexpanding type of dilator but the bag is very difficult for some people to swallow. After the largest degree of dilation is reached, the patient is instructed to return when he feels the need of another dilation.

Mosher[13] passes his pneumatic dilator under fluoroscopic guidance. The instrument is coated with barium. It is passed through the cardia, the position being judged by the appearance on the screen. When in place the usual inflation is carried out.

Jackson[14] also uses the Mosher pneumatic dilator and stresses the importance of properly placing the instrument. At least the first dilation is done under the fluoroscope, so that an accurate measurement can be taken from the point of constriction to the upper teeth. To facilitate the taking of this measurement the dilator is calibrated in centimeters from the middle of its bag upward. When the apparatus is in such a position that, on inflation, the constriction of the bag is seen to be exactly in its middle, the measurement at the patient's upper teeth is read and recorded for subsequent placement of the dilator. The average measurement has been found to be 40 cm., the shortest 33 cm., and the longest 50 cm. In order to insure proper placement of the dilator some workers prefer to introduce it through an esophagoscope.

Once the dilation is accomplished, the after-treatment is quite important. It should be remembered that, especially in the long standing cases, the esophagus will be dilated and perhaps diseased. Therefore, careful regulation of the diet is indicated, no overloading of the esophagus may be permitted, and in some cases local treatment through the esophagus must be carried out. If the esophagus is very much dilated and constantly contains stagnated food remnants, daily irrigations with warm saline solution are very beneficial.

Occasionally, the dilatation and distortion of the esophagus will be so great that no thread will go through to be used for the passage of a bougie. On esophagoscopy the attempt to find the cardia may also be unsuccessful. Under such circumstances, if dysphagia is severe, a gastrostomy is indicated in order to permit correction of the hunger and dehydration. Once these symptoms are overcome one of several plans may be adopted. At times, it has been found feasible to carry out manual dilatation of the cardia from below. If this cannot be done, a retrograde esophagoscopy may be performed. Once the passageway has been found, a bougie is passed upward to the mouth. This is used to draw a thread into the stomach, and out through the abdominal wound. The thread is then kept in place and used either for retrograde bouginage or for guiding bougies passed from the mouth as recommended by Plummer.[15]

In the great majority of cases symptomatic relief can be obtained by the methods of dilation just described without great risk to the patient. In case of failure, or because of severity of symptoms, operation may be considered.

Some authors have never found it necessary to operate. Gray and Skinner[16] stated recently, that in over 1,200 cases of cardiospasm seen at the Mayo Clinic operations for the relief of cardiospasm were performed only seven times. The procedures consisted of the Mikulicz operation of manual dilation of the cardia, four times, esophagogastrostomy, once, thoracocervical sympathectomy, once, and abdominal sympathectomy combined with manual dilation of the cardia, once.

Operation is undertaken only for a very definite indication:

(1) To bring about relief in those cases in which dilation has failed.
(2) In the hope of bringing about more permanent symptomatic relief than is usually obtained after instrumental dilation.
(3) To try to remedy the cause of the disability.

The simplest operations are those designed for symptomatic relief by establishing better drainage of the esophagus. Various procedures have been devised, some of which have been given up because they proved dangerous or ineffective. Those most commonly employed at the present time are freeing of the cardia and lower esophagus, combined with instrumental dilation from above; manual dilation from below through a gastrotomy; or transperitoneal esophagogastrostomy.

To expose the region an epigastric incision is made just to the left of the median line and carried upward into the angle between the ensiform and the costal margin. It is rarely necessary to perform an osteoplastic resection of the costal arch. The left lateral ligament of the liver is divided and the under surface of the diaphragm exposed. Eggers[17] operated upon three cases by this method. The cardia and the lower esophagus were completely freed out of their bed. A tape was passed around the esophagus and all connective tissue strands, blood vessels and nerve fibers surrounding it were divided until the longitudinal fibers of the esophagus could be followed down onto the wall of the stomach. By gentle traction the esophagus could be palpated well up into the mediastinum. There was no abnormal thickening or infiltration noted. The wall was soft throughout and there was no sudden transition from the dilated to the narrow portion, or at the entrance of the esophagus into the stomach. A large stomach tube was passed without difficulty. Exploration of the abdomen revealed extensive adhesions from former operations in one case, and an old duodenal ulcer and a patent gastro-enterostomy in another case. Whether they could be held responsible as etiologic factors is questionable. In one patient, Eggers performed a gestrotomy and manual dilation of the cardia in addition to the above procedure. A one-inch incision was made in the anterior wall of the stomach between traction sutures. The stomach was emptied by means of suction, and a finger then inserted for exploration of the cardia. A small dimple was felt but the finger did not enter the esophagus until gradual pressure had been exerted. The index finger was inserted and then the middle finger. The cardia was stretched in all directions until it admitted two fingers. Stretching with two fingers simultaneously was not very successful on account of the depth. Considerable food remnants were found in the esophagus in spite of the fact that it had been irrigated prior to operation. These were removed by suction. The incision in the stomach was closed with two rows of sutures. The convalescence was uneventful. This patient was entirely relieved of all his symptoms, and gained 30 pounds in weight. Reexamination of his esophagus, three years later, showed the condition of the esophagus to be unchanged, with identical roentgenologic evidence of cardiospasm, and no diminution in the size of the esophagus in spite of complete symptomatic relief (Fig. 4).

Several authors have commented on similar observations, notably Stubbe[18] and Stephens.[19] The latter reported ten cases treated with dilation, in only two of which decrease in size of the esophagus was noted. There is at present no adequate explanation for the symptomatic relief without appreciable change

in the roentgenographic appearance of the esophagus. One is forced to the conclusion that the mechanical dilation does not "cure" the condition, but simply results in diminishing the resistance of the cardiac sphincter to the passage of food.

In patients with marked elongation and sacculation of the esophagus, in whom the secondary mechanical factors are perhaps more important than the

FIG. 4.—1935—Cardiospasm before operation.
1938—Cardiospasm three years after manual dilation of cardia. Complete symptomatic relief with gain of 30 lbs. in weight. Roentgenologic appearance of esophagus unchanged.

original achalasia, esophagogastrostomy offers the best results. It may be performed through the thorax, but has been given up by most surgeons because of inaccessibility or danger of empyema. Heyrovsky[10] is credited with the development of the operation by the abdominal route. Collected statistics by Fromme,[20] and Häggström[21] show a negligible mortality, and good functional results. After freeing the cardia and esophagus through a high epigastric incision as described, the dilated portion must be drawn down through the hiatus before an anastomosis can be safely performed. The hiatus may have to be widened and the crura of the diaphragm divided. Several operations employing a technic similar to Finney's pyloroplasty have been described within the last few years. Churchill,[22] and Womack[23] have each reported successful cases. The operation should be considered a serious one and not be undertaken lightly. It finds its greatest application in patients whose esophagus is elongated and sacculated.

Longitudinal incision of the musculature similar to Rammstedt's operation on the pylorus has been recommended by Heller,[24] and favorable results have

been reported by numerous writers. The many observations of the absence of an anatomic sphincter, or any abnormal thickening, make it appear that there is no indication for a plastic procedure, and that an incision of the musculature carries the risk of perforation.

Operations aimed not alone at symptomatic relief, but which are intended to try to remedy the cause of the disability have been developed since the experimental work of Hurst,[8, 25] and Knight,[3] and others, called attention to the importance of disturbances of the neuromuscular mechanism of the cardia in the production of cardiospasm or achalasia. Knight himself performed the operation, based upon his experimental work, on four patients, but the results do not seem to have been as satisfactory as had been anticipated. W. A. D. Adamson, of the Royal Infirmary, Edinburgh, and G. E. Gack of St. Bartholomew's Hospital, London, have each performed the operation upon four patients (quoted by Knight[3]); in none of these are late reports available. In this country, Eliason and Erb[26] have operated upon two cases by the method advocated by Knight. A sympathetic denervation of the cardia was undertaken by excising a portion of the left gastric artery with its surrounding fat and nervous tissue. The first case was materially benefited, symptomatically; the second one, to a lesser degree. In neither case was the size of the esophagus perceptibly reduced.

Craig, Moersch and Vinson,[27] of the Mayo Clinic, performed a bilateral resection of the cervicothoracic trunk and ganglions, in a patient in whom ordinary methods of treatment had failed, and in whom dysphagia and severe pain were the outstanding symptoms. Preliminary tests were made which indicated to the authors that permanent relief of pain might be effected following removal of the sympathetic ganglia. Posteromedian incisions were made extending from the tip of the fifth cervical spine to the tip of the fourth thoracic spine. After resecting a portion of the transverse process and the first rib the posterior mediastinum was entered. The cervicothoracic sympathetic trunk and ganglia were removed on both sides. A bilateral operation was performed more fully to denervate the esophagus and to equalize the rise in surface temperature of the skin of both arms and both sides of the face. From a cosmetic standpoint also, the bilateral operation is preferable since it produces a bilateral Horner's syndrome. The patient's postoperative course was uneventful, and the wound healed perfectly. Following operation, she was completely relieved of dysphagia, and of the residual type of pain, and she has had no further paroxysmal attacks of the acute type of pain.

With the present state of our knowledge and on the evidence submitted so far, it does not seem justified to advocate extensive operations on the sympathetic nervous system. As Bird[28] states, from the work of some of these authors it seems unlikely that any operation of reasonable magnitude will effectively remove the sympathetic supply to the cardia. Furthermore, it seems doubtful that denervation will benefit patients with advanced degrees of the disease in which the mechanical factors are prominent. Instrumental dilation offers the best chance of relief in the majority of cases. Only on those in whom it

fails or who are too far advanced may one of the procedures aimed at establishing better drainage be instituted.

From a study of the modern literature one gains the impression that a disturbance of the neuromuscular mechanism of the esophagus and more particularly of the cardia, is responsible for the symptom-complex of cardiospasm. There is no other way to explain the diffuse dilatation with obstruction at the lower end in the absence of an anatomic sphincter. No other esophageal obstructions, whether due to carcinoma, fibrous stricture, or other lesions of long duration are associated with nearly the degree of dilatation which is observed in cardiospasm. The fact that in the great majority of cases the esophagus does not return to normal after establishing improved drainage, likewise, supports this view. One has to assume the existence of a nerve lesion which affects the fibers of the esophagus itself and permits dilatation, and at the same time keeps the cardiac end closed, whether by spasm or achalasia.

If this conception is correct, one is justified in the assumption that the disease which causes cardiospasm probably has preceded the fully developed condition for which the patient is referred to an endoscopist or a surgeon. It may be a terminal condition in which the greater amount of damage to the nerve mechanism has already been done. One may liken it to acute poliomyelitis, in which the acute disease of the spinal cord is of short duration and has usually subsided at the time neurologists and orthopedists are called in to treat the resultant damage.

Assuming this course of events, it becomes evident that any treatment intended to be curative, would have to be administered earlier than is now usually the case. We should know the underlying etiologic factor causing the neuromuscular disturbance, whether it be inflammatory or nutritional. Deficiency of Vitamin B_1 has been held by some writers to be responsible. It is along this line that profitable research may be directed.

In the meantime, symptomatic relief can be brought to the great majority of patients by means of dilation of the cardia, either mechanical, from above, or rarely, manual, from below. Neither procedure entails any undue risk.

REFERENCES

[1] Plummer, H. S.: Diffuse Dilatation of the Esophagus Without Anatomic Stenosis (Cardiospasm); A Report of 91 Cases. J.A.M.A., **58**, 2013–2015, 1912.

[2] Vinson, Porter P.: The Diagnosis and Treatment of Diseases of the Esophagus. Charles C. Thomas, Springfield, Ill., 1940.

[3] Knight, G. C.: Sympathectomy in the Treatment of Achalasia of the Cardia. Brit. Jour. Surg., **22**, 154 and 864, 1934–1935.

[4] Mitchell, G. A. G.: The Nerve Supply of the Gastro-Esophageal Junction. Brit. Jour. Surg., **26**, 333, 1938–1939.

[5] Jackson, Chevalier: The Diaphragmatic Pinch-Cock in So-Called "Cardiospasm." Laryngoscope, **32**, 139, 1922.

[6] Barsony, T., and Wald, B.: Die Inspiratorische Hiatus Abschnürung bein Kardiaspasmus. Roentgenpraxis, **10**, 443, 1938.

[7] Mosher, Harris P.: The Liver Tunnel and Cardiospasm. Laryngoscope, **32**, 348, 1922.

[8] Hurst, Arthur F.: Achalasia. British Encyclopaedia of Medical Practice, Vol. **1**, London, 1936.

[9] Rake, G. W.: On the Pathology of Achalasia of the Cardia. Guy's Hosp. Reports, **7**, 141, 1937.

[10] Heyrovsky, H.: Casuistik und Therapie der Idiopathischen Dilatation der Speiseröhre, Oesophago-Gastro-anastomose, Arch. f. klin. Chir., **100**, 703–713, 1912–1913.

[11] Etzel, E.: Mega-esophagus and Its Neuropathology: A Clinical and Anatomico-pathological Research. Guy's Hosp. Rep., **87**, 158–174, 1937.

[12] Moore, Paul M., Jr.: Diagnosis and Treatment of Cardiospasm. Cleveland Clin. Quart., 103–108, April, 1940.

[13] Mosher, H. P.: Findings with the Barium Bougie in Cardiospasm. Am. Otol., Rhinol., and Laryngol., **36**, 1124–1134, 1927.

[14] Jackson, Chevalier L.: The Treatment of Cardiospasm: With Notes on Diagnosis and Etiology. Arch. Phys. Ther., X-ray, Radium, **15**, 172–174, March, 1934.

[15] Plummer, H. S.: The Value of a Silk Thread as a Guide in Esophageal Technique. Surg., Gynec. and Obstet., **10**, 519–523, 1910.

[16] Gray, Howard K., and Skinner, I. C.: The Operative Treatment of Cardiospasm. Journal of Thoracic Surg., **10**, 220, 1940.

[17] Eggers, Carl: Discussion of paper of Gray and Skinner.[16]

[18] Stubbe, H.: Oesophageal Achalasia Treated by Sympathectomy. Med. Jour. Australia, **24**, (2), 1001, 1937.

[19] Stephens, H. Brodie: Cardiospasm. Calif. and West. Med., **46**, No. 3, 1, March, 1937.

[20] Fromme, A.: Erfahrungen mit der Operation des Kardiospasmus. Arch. f. klin. Chir., **157**, 606–614, 1929.

[21] Häggström, P.: Zwei Fälle von Kardiospasmus und Oesophagus Dilatation, die mit Glücklichem Ausgang nach Heyrovsky operiert wurden. Acta. Chirug. Scandinav., **66**, 345–371, 1930.

[22] Churchill, E. D.: Oesophageal Surgery. Surg., Gynec., and Obstet., **60**, 417–423, 1935.

[23] Womack, W. A.: Esophagoplasty for Esophageal Achalasia. Surg. Clin. N. Amer., **18**, 1241–1254, 1938.

[24] Heller, E.: Extramuköse Cardiaplastik beim Chronischen Cardiospasmus mit Dilatation des Oesophagus. Mitt. a. d. Grenzgeb. d. Med. u. Chir., **27**, 141–149. 1913-1914.

[25] Hurst, Arthur F.: Some Disorders of the Esophagus. J.A.M.A., **102**, 582–587, 1934.

[26] Eliason, L. E., and Erb, W. H.: Cardiospasm; Report of Two Cases Treated by Resection of Sympathetic Supply to Cardiac Sphincter. Amer. Jour. Surg., **35**, 105–112, 1937.

[27] Craig, W. McK., Moersch, H. J., and Vinson, P. P.: Treatment of Intractable Cardiospasm by Bilateral Cervicothoracic Sympathetic Ganglionectomy: Report of a Case. Proc. Staff Meet. Mayo Clin., **9**, No. 50, 749, December 12, 1934.

[28] Bird, Clarence E.: Recent Advances in Surgery of the Esophagus. Surgery, **6**, No. 4, 622–631, October, 1939.

Read before the New York Surgical Society, October 23, 1940.

THE MANAGEMENT OF APPENDICEAL PERITONITIS—WITH SPECIAL REFERENCE TO THE OPERATIVE HANDLING OF THE LOCALIZED ABSCESS

LeGrand Guerry and George T. McCutchen, M.D.

Columbia, South Carolina

Since the original paper on the deferred treatment of peritonitis of appendiceal origin by A. J. Ochsner[1] there has been a rather intense controversy on this subject. It is safe to say that most observers have seen fit to reject his ideas altogether; but some have accepted them and have applied them with considerable success. This latter group, during recent years, has been able to win adherents by their continual insistence that there is a great deal of virtue to the deferred treatment when applied to particular cases of appendiceal disease, specifically the ruptured group and more specifically certain well-defined cases of the ruptured group. We shall attempt to define the groups in which we believe a gratifying reduction in mortality can be brought about.

Interpretation of the Ochsner Treatment.—Some of the difficulty encountered by advocates of the deferred treatment in discussing their views has come from the variety of interpretation put upon the Ochsner treatment. We find, in interviewing many observers and in reviewing the literature, that there is little uniformity of interpretation. A clear-cut definition of Ochsner's[1] idea may be found in a few words in his "Handbook of Appendicitis." He states: "The temperature was 104° F.; pulse 140; abdomen enormously distended; features pinched. My experience with this and similar cases had taught me that whenever I operated upon patients approximately in this condition, the patient invariably died.

"Some years ago, before I had learned to appreciate the treatment which I describe, I frequently operated upon patients in just this condition as a last resort, thinking that this gave them the only possible chance of recovery. Since then I have learned that this case belonged to a class which practically never recovered after an operation, if it is performed while the condition is that in which I found this patient; and of which a very large majority recover if the treatment (delayed) is followed which I have described ——"

These statements represent the basic idea of his principle, and there has been no divergence from this principle by his modern day adherents. Changes in this principle, if they have been made, are in the nature of refinements of application of this basic fundamental. We shall attempt to clarify some of these refinements. Let us make it clear in the beginning that we believe that there can be no contention over the idea that immediate operation is the only form of treatment for acute, unruptured appendices. Though it may be deemed unnecessary, we make this statement especially strong because there are some who believe that the advocates of the deferred treatment would defer operation in all cases of appendicitis. If cases of appendicitis presented them-

selves and were operated upon before rupture occurred there would be no need for the discussion we are now presenting. We are still faced with the fact, in spite of intensive public education, that Bower[2] in 5,000 cases found that 44 per cent of patients suffering from appendicitis have peritonitis on admission to a hospital. Foss[3] encountered 46.5 per cent of peritonitis in

FIG. 1.

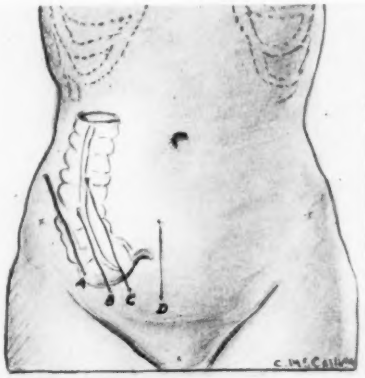


FIG. 2.

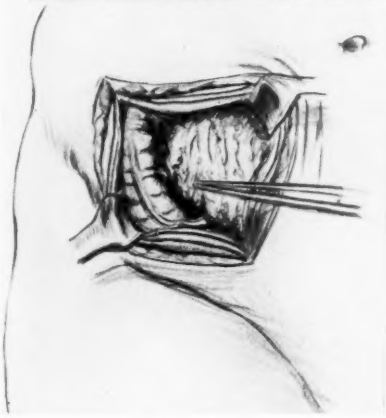


FIG. 3.

FIG. 4.

FIG. 1.—The location of some of the incisions used in cases of abscess. Incision B is probably the one most commonly required. The variation in the situation of these incisions serves to illustrate the point that strict individualization is the most important factor in the selection of site of incision.

FIG. 2.—Illustrating the degree of exposure which should be obtained if the incision is adequate.

FIG. 3.—Illustrating the extreme degree of exposure of the contents of the right lower quadrant which it is possible to obtain through an "extensive" McBurney incision.

FIG. 4.—This is a complementary illustration to Figure 3, and shows the use of Mikulicz pads to exteriorize the cecum and abscess.

1,000 cases on admission to the hospital. Keyes[4] found that 50.3 per cent of 495 cases had peritonitis on admission to the hospital. Alton Ochsner[5] reports the astounding percentage of 78.7 in a series at Charity Hospital in New Orleans. So with Hamilton Bailey[6] we say that, "With the advent of that Elysium when all cases of acute appendicitis are in the hands of the surgeon when the disease is still limited to the appendix the need for the Ochsner (delayed) treatment will pass."

The interpretation put upon the Ochsner treatment in England, by Sherren,[7] was that all ruptured cases should be deferred, even those with a localized abscess, until complete resolution had taken place and recommended removal of the appendix during a "well interval" several months after resolution. Of course, he and his adherents encountered cases in which resolution

FIG. 5. FIG. 6.

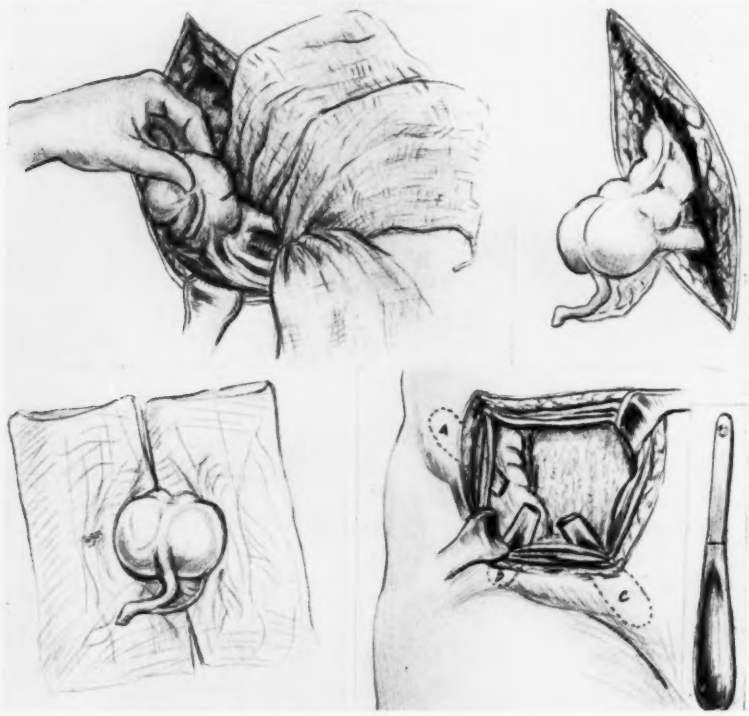


FIG. 7. FIG. 8.

FIG. 5.—Illustrating the exposure of an appendix lying directly posterior to the head of the cecum. The exposure is accomplished by rotation of the head of the cecum forward.

FIG. 6.—Illustrating the delivery of the head of the cecum with the appendix from the abdominal cavity. This degree of motility is frequently attainable, especially in thin or visceroptotic subjects. Delivery of the cecal head with the appendix is attainable in the large majority of patients.

FIG. 7.—Illustrating the exteriorization of the operative field with gauze pads after delivery of the cecum and appendix. This affords protection against soiling in the event that the appendix is ruptured during removal in the acute, nonruptured cases.

FIG. 8.—It will be noted that the omentum has been tucked down around the medial aspect of the head of the cecum and over the small intestine down on to and over the brim of the pelvis. All drains are placed exterior to this omental "sheet."

would not take place; and in these instances incision and drainage of the abscess was recommended with removal of the appendix sometime later. This same interpretation has been applied by men in this country with a reduction in their mortality. At another extreme, some have applied the deferred treatment to a restricted group which includes only those cases in shock or near *extremis,* with an acute peritonitis, in whom supportive treatment

is given until the general condition of the patient can be improved somewhat; but waiting is not continued until localization of the peritonitis before operative intervention. Our position is a sort of middle ground. We have found through experience that cases with diffuse peritonitis will go on to localization if they can be tided over the period of profound toxemia, and,

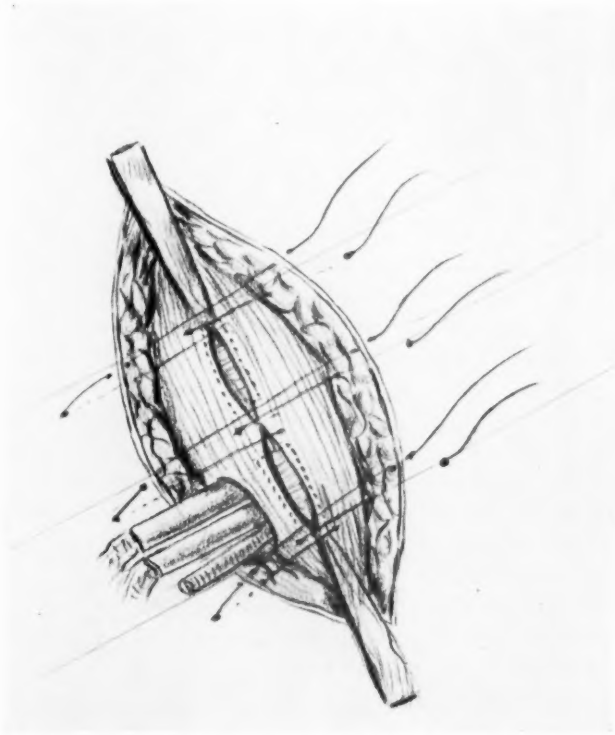


FIG. 9.—Illustrating the closure of the fascia of the external oblique fascia and skin.

therefore, we wait for this localization. However, we do not go so far as the Sherren group. We do not wait for complete resolution of a localized abscess, but prefer to operate during the stage of abscess. We adhere to this latter idea because we believe that the waiting necessary for complete resolution carries a patient into the period of danger from ascension of infection through the portal system, spontaneous rupture of a distended abscess cavity through its protective wall into the general cavity, septicemia, and other complications attendant upon the prolonged presence of an abscess anywhere in the body. We are certain that the reason for very prolonged waiting is, as Braddon[8] puts it, the fear of "the tragedy of conversion of a localized abscess into a general peritonitis." The mortality produced by prolonged waiting overbalances the mortality in our series of abscess cases which have been operated upon. Since this experience has not been universal, we have been

forced to the conclusion that there must be some particular virtue in our method of handling the abscess case. We have, therefore, incorporated a detailed description of the operative technic employed by us in this group in the discussion of the deferred treatment; because, we cannot help but believe that it has served as a very important part and parcel of the results accomplished by us with the deferred treatment.

Rationalizing the Principle of Waiting.—The principle of deferred operation has a great deal of precedent in the handling of other surgical conditions. The ideas to which we now adhere so strongly in regard to the management of empyema, gonococcic infection of the fallopian tubes, and infections of the hand with lymphangitis, were arrived at through a long process of trial and error and through antagonism almost as intense as that against the deferred treatment of the ruptured appendix. It was not until the experience in the handling of empyema which the World War afforded, that we became convinced that the proper method of treating a pleural effusion following pneumonia was to wait until the acute exudative process was over, the pus in the pleural cavity had become thick, and the patient had been allowed to develop some immunity to the infection. Early in this century an acute gonococcic infection of the tubes and adjacent pelvic peritoneum was considered ripe for immediate operation. Through a gradual process of study we have now come to the opposite conclusion—that operation should be delayed in gonococcic pelvic inflammatory disease. We have learned that immunity will be established, and that the patient is a much less serious operative risk during a more quiescent stage of the disease. Infections of the hand with lymphangitis, are now deferred until localization is complete, and some immunity is established.

Comparative statistics of our own appear to us convincing. In a series of 94 cases with diffuse peritonitis, which were immediately operated upon, ten died, a mortality of 10.64 per cent. In 139 cases of acute diffuse peritonitis treated conservatively and operated upon later, there were two deaths, a mortality rate of 1.43 per cent. We feel that this comparison alone should serve to lift the proposition of deferred treatment from the category of supposition to the realm of established fact. Coller and Potter[9] report their mortality rate in acute appendiceal peritonitis with immediate operation as 52 per cent. With the adoption of the deferred treatment they were able to reduce their mortality to 8.6 per cent. This is the most striking statistical evidence we have discovered. Deaver and Magoun[10] report 1,358 cases of acute appendicitis operated upon between the years 1901 and 1905 with a mortality rate of 10.5 per cent. In all of these cases the patient was immediately operated upon when seen. In 1910, the deferred treatment was adopted for all indicated cases, and from 1910 to 1914 there were 1,385 cases with 52 deaths, a 3.7 per cent mortality. Walker[11] reports a series of 30 cases treated by deferred operation with four deaths, a mortality of 13 per cent, and compares it with a mortality of 42 per cent in 77 cases treated by immediate operation.

Technic of Waiting.—As was stated above, we advocate deferring operation in those cases who are first seen when they are in a stage of diffuse peritonitis. This condition may be present: (1) A few hours after onset of appendiceal disease in those cases which go on to perforation rapidly; (2) in some cases many days after the onset of appendiceal disease where the perforation was successfully localized immediately, but continued growth of the abscess has allowed it to break through its protecting barriers into the general peritoneal cavity; (3) those cases in which evidence of diffuse peritonitis appears three to four days after onset of appendiceal disease. Parenthetically, we may say that the latter group is the most common one, but we would like to deemphasize the phrase "third to fourth day cases" which so commonly appears in the literature. This phrase is confusing because it denotes a rule of thumb in a condition where strict individualization of cases is necessary. As we shall go on to show and attempt to illustrate, the deferred treatment is indicated in all cases of rupture with diffuse peritonitis whether this complication has supervened hours, days, or weeks after the onset of symptoms.

Operation in either of the three groups cited should be deferred until evidence of localization takes place. The symptoms of peritonitis, distended and rigid abdomen, rapid pulse, high temperature, prostration, and hippocratic facies will gradually disappear in the course of a few days, and the patient will present a picture of localized abscess and satisfactory general physical status. When this latter status is accomplished, operative drainage of the abscess and removal of the appendix is indicated. Let us state again that, contrary to the attitude of some advocates of the Ochsner principle, we do not wait for complete resolution of the abscess. We realize fully that this resolution will take place in the majority of cases; but this prolonged waiting is fraught with danger of complications far greater than the danger of a gently and expeditiously executed operation upon the abscess. The above three groups are the only ones in which we believe that operation should be deferred for any appreciable length of time. There are many cases that when first seen have some suspicious evidence of perforation but in whom the evidence of peritoneal irritation is local. These cases should not be deferred. Cases where one can be reasonably certain that perforation has taken place recently but the signs of peritonitis are local should not be deferred. Cases which are first seen after a localized abscess has definitely formed should not be deferred. The citation of illustrative cases will serve to clarify the statements of this paragraph, and also give a more concrete and workable knowledge for use in individualizing cases.

ILLUSTRATIVE CASE REPORTS

Case 1.—J. G., male, age 17, was admitted to Columbia Hospital, October 15, 1937, stating that generalized abdominal cramps had begun three hours before admission. He took a large dose of epsom salts on his own initiative shortly after these pains began. At the time of admission his temperature was 103.5° F., pulse 110; the abdomen markedly distended, tender and rigid throughout. The facial expression was typically

"washed-out." He was vomiting frequently and profusely. Intravenous saline and glucose were begun and administered in adequate amounts for six days. (The continuous intravenous drip serves admirably to furnish fluids to these patients over a period of days.) A Bartlett apparatus attached to a Levine tube in the stomach was used for continuous decompression. Large doses of morphine were given as indicated for pain and restlessness. Six days after admission the temperature was 100° F., the pulse rate normal, the facial expression good, and the distention, generalized rigidity and tenderness had disappeared. The intravenous fluids and continuous gastric suction were discontinued and he was able to take fluids and a light diet. A palpable mass was apparent in the right lower quadrant, and rectal examination revealed an inflammatory mass in the cul-de-sac. (The appearance of diarrhea in patients with peritoneal suppuration so frequently indicates a cul-de-sac accumulation. Rectal examinations should be made at indicated intervals to aid in determining the operative approach.) On October 26, 1937, operation was performed through a low, extensive McBurney incision. The appendix was removed and the cul-de-sac abscess and that in R.L.Q. were drained. The postoperative course was relatively uneventful.

This case is cited to illustrate some features of the supportive treatment of patients during the process of waiting; but more particularly to illustrate the possible sudden onset of evidence of general peritonitis with its accompanying prostration. This patient had been suffering with abdominal pain only three hours before he was first seen. Such rapid progress of appendiceal disease to the point of rupture and general peritonitis is unusual.

Case 2.—J. E., male, age 16, was admitted to Columbia Hospital, February 5, 1935, with a history of abdominal discomfort beginning three days previously. The pain became progressively worse and he had become distressingly sick during the previous 12 hours. Vomiting had been prominent, and at the time of admission to the hospital the temperature was 103° F., pulse 130. The abdomen was distended and rigid. The facies bespoke the profoundness of the toxemia. He was vomiting copiously at frequent intervals. Treatment was instituted along the same lines described in Case 1. During the course of the next four days the evidences of profound toxemia disappeared, and a localized mass became palpable in the R.L.Q. After two more days localization was considered complete and operation upon the abscess performed.

This case is typical of those referred to in the literature as "third to fourth day" cases. This one was deferred because the evidence of profound toxemia had supervened and not because of the duration of the disease. The former should invariably be used as the criterion for deferring operation instead of the latter. Waiting should not last longer than the time necessary for localization and cessation of extreme toxemia to take place.

When speaking to the skeptical about the deferring of operation the question is quite naturally asked, "how many patients die while one is waiting?" In the series here reported, which includes 131 cases of acute diffuse peritonitis with profound toxemia, two died, a mortality of 1.52 per cent. This figure is measurably lower than those of observers advocating other methods whose material we have studied in the literature for comparison. The small percentage of mortality during the process of waiting seems to weigh heavily in favor of our contention. It may be compared with our figure of 10.75 per cent, Coller's[9] 52 per cent, and Walker's[11] 42 per cent in cases operated upon immediately.

Case 3.—B. H. J., female, age 9, was admitted to Columbia Hospital, July 3, 1938, stating that abdominal pain had begun on June 29, 1938. Nausea and vomiting were not associated, and she was not incapacitated until July 2, 1938, when she was referred to the hospital. Examination revealed a palpable mass in the R.L.Q., with no abdominal distention. The temperature was 103° F., but the facial expression was good and general physical status excellent. With a diagnosis of appendiceal rupture, with abscess formation, operation was performed on the day of admission. An extensive McBurney incision was employed, the appendix removed, and the abscess drained. The postoperative course was relatively uneventful.

This case serves to illustrate that waiting is not practiced where localization has already taken place and the physical status of the patient is good. It also serves to illustrate that large group of cases in which rupture occurs and in which there is never any evidence of general peritoneal soiling. The omentum and anatomic position of the appendix, and slowness of spillage serve to keep the process localized from the very beginning. Other cases of this type will be cited for other features pertinent to the discussion.

Case 4.—H. S., female, age 9, was admitted to Columbia Hospital, July 7, 1938, with a history of vague abdominal pain of 24 hours duration. Associated diarrhea at the onset suggested a diagnosis of gastro-enteritis to her attending physician, and a definite diagnosis of appendicitis was not made until about 18 hours after onset of pain. Physical examination revealed a child in good general condition, with marked tenderness and rigidity in the R.L.Q. No distention or other evidence of diffuse spread was present. Temperature 101.5° F., pulse 110. A definite diagnosis of appendicitis could be made but the fact that rupture had occurred could be and was questioned. Operation was performed on the day of admission. Fluid with a distinct colon odor was found upon opening the abdomen through a McBurney incision. The appendix was found to be perforated near its tip with spillage fairly well walled-off by plastic lymph and omental adhesions. The appendix was removed and the abscess thoroughly drained.

This case was chosen because it is characteristic of that large group in which one may entertain considerable doubt that the appendix has ruptured. There is no reason to delay operation on these cases. Cases of this type have given rise to more contention than any other group, and serve as the main reason that a great many surgeons feel that they cannot accept the deferred treatment. This contention has been caused more by misunderstanding than by disagreement.

Two cases (Nos. 5 and 6) have been taken from our files to illustrate our belief that prolonged waiting for resolution of the abscess is dangerous:

Case 5.—W. C., male, age 13, was admitted to Columbia Hospital, September 23, 1938, with the history that six weeks before admission he had suffered an attack of abdominal pain, with nausea and vomiting which cleared up to some extent although he had been incapacitated for work or play since the onset. Three days before admission he became acutely ill again and arrived at the hospital *in extremis*. He was intensely jaundiced, the abdomen was markedly distended and tender. He expired two days after admission. No operative procedure was attempted because of his very poor general condition. Autopsy revealed a ruptured, gangrenous appendix, with a huge pelvic abscess which had ruptured into the general peritoneal cavity, a blood stream infection with metastatic lung abscess, acute vegetative mitral valvular endocarditis, and marked cloudy swelling of the liver.

This case illustrates the danger of leaving an abscess of appendiceal origin for a prolonged period. This patient's outlook for recovery would have been good if he had presented himself a few days after rupture, or even a week or ten days before he did apply for treatment. As we have stated, there is a considerable amount of literature appearing to-day which tends toward the attitude that prolonged waiting for complete resolution is the procedure of choice. We voice the result of our experience that it is a procedure the danger of which greatly outweighs that of a properly executed operation upon the well-formed abscess. The English advocates of prolonged waiting state that the unfavorable eventualities can be obviated by observing these patients in "the very shadow of the operating amphitheatre"; but we find it difficult to conceive of their being able to recognize an "impending" spread of the infection into the blood stream or the rupture of a culdesac abscess into the general cavity. One of our colleagues has observed the rupture of a cul-de-sac abscess during abdominorectal examination.

Case 6.—H. B., male, age 21, was admitted to Columbia Hospital, August 8, 1938, with a definite history of an acute attack of appendicitis four weeks previously. He assumed that the attack had subsided uneventfully when the nausea, vomiting and severe abdominal pain disappeared. He continued his participation in the activities of a summer camp until a few days before admission, when he noticed a tender mass in his right lower quadrant. (This is not unusual; we see an occasional patient who is ambulatory with a circumscribed appendiceal abscess.) At operation he was found to have a well-defined appendiceal abscess. There was also extensive destruction of the head of the cecum, which feature makes this a case in point. It was necessary to resect a part of the cecum to get above this diseased portion. He developed a cecal fistula which has just been closed at the time of this writing, one year later. We attribute the destruction of the head of the cecum to the fact that the infection was allowed to dissect between the layers of the cecum. We have seen this condition in other cases which were allowed to wait for prolonged periods.

We believe that the two cases above cited illustrate adequately the danger of prolonged waiting, which leads one to the belief that this danger is more real than imagined. We would like to avoid being controversial on the issue of prolonged waiting. We accept the fact that all but about 25 per cent of cases with appendiceal peritonitis will go on to complete resolution. It is in this remaining 25 per cent where operation is "forced" (Lehman[12]) that the danger of complications which we have described outweighs the danger of operating upon a well-circumscribed abscess, when it appears. This should not be made an issue among those advocating the deferred treatment because it detracts from the strength of their stand on the main issue, that is, the deferring of operation upon the patient with diffuse peritonitis until he has been tided over the "critical" stage of his illness.

Technic of Operation upon Appendiceal Abscess.—We go into some detail, perhaps unnecessarily, in the accompanying illustrations in an attempt to define the operative approach and handling of appendiceal abscess. We feel that this type of surgery, like any other, depends in large part for its success on scrupulous attention to detail: First, the location of the incision should

be made directly over the abscess to avoid traversing unsoiled viscera as much as possible. Second, the extent of the incision should provide adequate working room to promote gentleness and facility of execution of subsequent steps. Third, mobilization of the head of the cecum is important. We emphasize this because this maneuver relieves us of the necessity of "rooting" for the appendix, removing it retrograde, and using other procedures which bespeak inadequate "control" of the operative field. Fourth, the adjacent areas should be protected from soiling. The necessity for this is evident; we have attempted to describe its accomplishment in the legends. Fifth, adequate drainage should be employed. For this purpose we use cigarette and split, fenestrated soft rubber tubing which is never placed between coils of small intestine. Sixth, the placing of the omentum preliminary to closure is highly important. This should be done so that the abscess area is exteriorized as much as possible, and so that the drains are not in contact with the small intestine. Seventh, the closure of the wound is done loosely. The wound is always potentially, if not actually, infected. By delivering the drains through stab wounds we try to avoid the occurrence of postoperative hernia.

TABLE I

SUMMARY OF MORTALITY STATISTICS IN 3,795 CASES OF APPENDICITIS

		No. of Cases	No. of Deaths	Mortality Percentage
(1)	Recurrent appendicitis	1,572	0	0
(2)	Acute appendicitis	989	1	0.10
(3)	Acute, gangrenous, ruptured appendix, with localized abscess	545	3	0.55
(4)	Acute, gangrenous, ruptured appendix, with diffuse peritonitis —immediate operation	94	10	10.64
(5)	Acute, gangrenous, ruptured appendix, with diffuse peritonitis —deferred operation	139	2	1.43
(6)	*In extremis*—drainage—appendix not removed	12	3	25
(7)	Appendix removed in course of other operations	444	0	0
	Totals	3,795	19	0.50

SUMMARY AND CONCLUSIONS

(1) Attention is called to the fact that the statistics detailed in Table I show the mortality incidence in a continuous, consecutive, unselected series of cases of appendicitis, extending over a period of more than 35 years. During this period a mortality of around one-half of one per cent has been sustained. A fact which, in itself, is most significant.

(2) We regard the deferred treatment in the cases in which it is indicated as the first step in the operative procedure, and in no way is it regarded as a substitute for operation.

(3) There is abundant evidence, both clinical and experimental, to prove the unmistakable tendency toward localization in cases of appendicitis complicated by the presence of pus.

(4) There is an optimum time for operating upon every surgical patient. The great problem of surgical judgment is to be able to select that time.

The greatest ally the surgeon has in these critically ill patients is their amazing defense mechanism.

REFERENCES

[1] Ochsner, A. J.: A Handbook of Appendicitis. G. P. Engelhard & Co., Chicago, Ill., 1902, p. 110.

[2] Bower, J. O.: Acute Appendicitis in Philadelphia. Monthly Bulletin Dept. Public Health, Philadelphia, Pa., December, 1932, pp. 2–16.

[3] Foss: Quoted from Ochsner.[5]

[4] Keyes: Quoted from Ochsner.[5]

[5] Ochsner, Alton: The Conservative Treatment of Appendiceal Peritonitis. New Orleans Med. and Surg. Jour., **67**, 32, July, 1934.

[6] Bailey, Hamilton: The Ochsner—Sherren (Delayed) Treatment of Acute Appendicitis. Brit. Med. Jour., **1**, 140, January 25, 1930.

[7] Sherren: Quoted from Bailey.[6]

[8] Braddon, P. D.: The Ochsner—Sherren (Delayed) Treatment of Neglected Appendicitis. Med. Jour. of Australia, **1**, 660, May 30, 1931.

[9] Coller, F. A., and Potter, E. B.: The Treatment of Peritonitis Associated with Appendicitis. J.A.M.A., **103**, 1753, December 8, 1934.

[10] Magoun: Quoted from Ochsner, Alton: Texas State Jour. Med., **32**, 579, January, 1937.

[11] Walker, I. J.: Immediate or Deferred Surgery for General Peritonitis Associated with Appendicitis in Adults. New England Jour. Med., **219**, 323, September 8, 1938.

[12] Lehman, E. P., and Parker, W. H.: The Treatment of Intraperitoneal Abscess Arising from Appendicitis. ANNALS OF SURGERY, **108**, 883, November, 1938.

[13] Ochsner, A. J.: The Feeding of Patients Suffering from Peritonitis Due to Appendicitis and Other Similar Causes. Louisville Monthly Jour. Med. and Surg., **6**, 300, February, 1900.

[14] Melly, J. M.: The Delayed Treatment of Peritonitis Complicating Appendicitis. Practitioner, **131**, 569, November, 1933.

[15] Priestley, J. T., and McCormack, J.: Generalized Peritonitis Secondary to Rupture of the Appendix. Surg., Gynec., and Obstet., **63**, 675, November, 1936.

[16] Arnold, H., and Gibson, L. V.: A Method of Handling Ruptured Appendices. Nebraska State Med. Jour., **20**, 211, June, 1935.

[17] Kehl, W., and Rentschler, C. B.: Acute Appendicitis Complicated by Peritonitis: Immediate and Late Results in 126 Consecutive Cases. Am. Jour. Surg., **29**, 373, September, 1935.

[18] Shute, F. C., Jr.: The Perforated Appendix. New Orleans Med. and Surg. Jour., **88**, 171, September, 1935.

[19] Cottis, G. W., and Ingham, H. W.: The Nondrainage Treatment of Peritonitis. New York State Jour. of Med., **35**, 49, January 15, 1935.

[20] Dorrance, G. M., and Nealon, S. W., Jr.: The Use of Cecal Drainage in Ruptured Appendicitis. New York State Jour. of Med., **35**, 119, February 1, 1935.

[21] Willis, J. C.: The Ruptured Appendix and Its Management. New Orleans Med. and Surg. Jour., **84**, 518, January, 1932.

[22] Marchini, F.: Abolition of Drainage in Circumscribed and Diffuse Peritonitis; Especially from Appendicitis. Arch. ital. di chir., **28**, 549, April, 1931.

[23] Gardner, C. E., Jr.: Delayed Operation in the Treatment of the Perforated Appendix. Surgery, **4**, 161, August, 1938.

[24] *Idem:* The Conservative Management of Appendiceal Peritonitis. Southern Med. Jour., **32**, 157, February, 1939.

[25] Cafritz, E. A.: Nondrainage of the Peritoneal Cavity in Appendiceal Peritonitis. J.A.M.A., **108**, 1315, April 17, 1937.

[26] Margottini, M.: Treatment of Acute Appendicitis and Peritonitis of Appendicitic Origin. Il Policlinico (sez. chir.), **45,** 88, February 15, 1938.

[27] Ladd, W. E.: Immediate or Deferred Surgery for General Peritonitis Associated with Appendicitis in Children. New England Jour. Med., **219,** 329, September 8, 1938.

[28] Willis, B. C.: The Treatment of Perforative Appendicitis with or without Abscess. Southern Med. Jour., **21,** 622, August, 1928.

[29] Altenkamp, T.: Treatment of Perforated Appendicitis with Serum. Der Chirurg., **9,** 930, December 15, 1937.

[30] Richard, A., and Asselin, J.: Twenty-four Cases of Appendicitis with Peritonitis—A Comparative Study of the Treatment and the Postoperative Course. Bull. et mém. Soc. nat. de chir., **56,** 1050, October, 1930.

[31] Decourcy, J. L.: Care of the Ruptured Appendix—Reduction of Mortality to Four Per Cent in Series of 50 Cases. Surg., Gynec. and Obstet., **56,** 756, December, 1936.

[32] Connell, F. G.: Drainage in Treatment of Perforated Appendicitis. Am. Jour. Surg., **41,** 255, August, 1938.

[33] Shipley, A. M.: The Treatment of Peritonitis Complicating Appendicitis. New England Jour. Med., **219,** 333, September 8, 1938.

[34] Domanig, E.: Treatment of Progressive Peritonitis Due to Perforation of Appendix. Wien. klin. Wchnschr., **51,** 906, August 26, 1938.

[35] Gurd, F. B.: A Specific Technique for the Treatment of Acute Perforated Appendicitis. Am. Jour. Surg., **17,** 52, July, 1932.

Idem: The Operative Treatment of Acute Appendicitis with Perforation. Canad. Med. Assn. Jour., **27,** 360, October, 1932.

[36] Lipskij, J.: Results of Therapy for Peritonitis Due to Appendicitis. Chir., **12,** 231–238, November, 1931.

[37] Shipley, A. M., and Bailey, H. A.: Treatment of Appendicitis Complicated by Peritonitis. Annals of Surgery, **96,** 537–550, October, 1932.

[38] Prochnow, F.: Serotherapy of Appendicular Peritonitis. Arch. f. klin. Chir., **174,** 349, February 18, 1933.

[39] Bauer, G.: The Treatment of Appendicitis Peritonitis. Acta chir. Scandinav., (Supp. 24) **70,** 1, 1933.

[40] Stowers, J. E.: Treatment of Acute Appendicitis in Its Two Phases—Before and After Perforation. Jour. of the Missouri State Med. Assn., **28,** 531, November, 1931.

BILE PERITONITIS

REPORT OF EIGHT CASES

CHARLES W. MCLAUGHLIN, JR., M.D.

OMAHA, NEBR.

FROM THE DEPARTMENT OF SURGERY, UNIVERSITY OF NEBRASKA COLLEGE OF MEDICINE, OMAHA, NEBR.

BILE PERITONITIS is the resultant peritoneal reaction caused by a variable amount of free bile within the peritoneal cavity. During the past 40 years, German and French observers have published on this topic a very extensive literature dealing, primarily, with the so-called idiopathic types of biliary peritonitis. Since 1920, a number of American investigators have reported observations on experimentally produced bile peritonitis in animals, but American and British literature still contains little on the clinical aspects of this condition. For example, two monographs on diseases of the liver and biliary tract by American authors, published in the past fifteen years, have no reference to bile peritonitis.

The treatment of eight such cases during the past six years, together with a detailed investigation of this subject, forms the basis of this paper.

CASE REPORTS

Case 1.—A male, age 68, was admitted to the University Hospital, with a slight clinical jaundice, and a history of recurrent calculous cholecystitis. The gallbladder was not visualized roentgenologically. Calculous cholecystitis was demonstrated at operation; the common duct was normal. A cholecystectomy without drainage was performed. Convalescence was stormy and lobar atelectasis, abdominal distension, and ascites developed. On the twelfth postoperative day a small incision was made in the right lower quadrant. Normal appearing bile drained copiously for two weeks, but gradually ceased by the twentieth day. On the fortieth postoperative day a right subdiaphragmatic abscess was evacuated of two liters of infected bile. Recovery was prompt, and the patient was discharged on the seventy-sixth day.

Case 2.—A female, age 76, was admitted to the University Hospital, with a history of recurrent calculous cholecystitis over a period of 30 years. Jaundice had occasionally been present, the attacks accompanied by chills and fever. Jaundice was not present on admission. No gallbladder shadow could be demonstrated roentgenologically. Chronic calculous cholecystitis was found at operation. The common duct was not dilated and no stones were palpated. Cholecystectomy was performed, with drainage of the gallbladder fossa. Twenty-four hours later abdominal pain, distension, fever and tachycardia developed, and profuse drainage of bile was noted along the abdominal drain. The patient appeared gravely ill and failed rapidly; she expired 48 hours postoperative. Postmortem examination disclosed 1,000 cc. of bile in the peritoneal cavity. A stone one centimeter in diameter was firmly impacted in the ampulla of Vater. No definite site of perforation was demonstrable in the common duct, cystic duct stump, or gallbladder fossa. *Pathologic Diagnoses:* Bile peritonitis; common duct stone; and pulmonary atelectasis.

Case 3.—A female, age 48, was admitted to the Methodist Hospital, with acute calculous cholecystitis of three days' duration. Exploration revealed an empyema of the gallbladder, with beginning gangrene of the wall. A cholecystostomy was performed; no stones were found in the gallbladder. The patient made a satisfactory recovery except

for a persistent mucous fistula. Six months later a cholecystectomy was performed and a stone found firmly lodged in the ampulla of the gallbladder. The common duct was not enlarged and no stones were palpable in it. The gallbladder fossa was drained. Sixty hours later abdominal pain, distension, fever, and tachycardia abruptly developed, and the patient appeared to be in surgical shock. There was profuse drainage of bile along the abdominal drain. Rapid circulatory failure followed, with death 18 hours after onset of the complication. No postmortem examination was permitted, but death certainly was due to bile peritonitis, resultant either from a slipped cystic duct ligature or an overlooked common duct stone, with perforation of the biliary tree.

Case 4.—A female, age 53, was admitted to the Immanuel Hospital, with a history of chronic calculous cholecystitis of ten years' duration, but with no jaundice. The gallbladder was not visible roentgenologically. A chronically diseased gallbladder was found at operation, with a stone firmly impacted in a very short cystic duct. Cholecystectomy was carried out, and the cystic duct stone removed. A small incision made in the common duct, to permit removal of the stone, was closed with interrupted sutures. The abdomen was closed, with drainage. Thirty-six hours later a definite and rapidly increasing tachycardia developed; the pulse increased gradually from 100 to 170, with no accompanying fever, pain, distension, air hunger, or altered blood pressure, although the patient's appearance was one of anxiety. The drain was shortened, and a profuse outpouring of bile promptly resulted, which continued for several days and then gradually decreased, while the patient appeared progressively better. Biliary drainage had ceased at the time of dismissal, 15 days postoperative. Biliary leakage in this case undoubtedly occurred through the incision in the common duct.

Case 5.—A female, age 27, was admitted to the University Hospital, 16 days after a cholecystectomy, performed in another institution. The common duct had not been explored and the abdomen was closed without drainage. Four days after operation severe upper abdominal pain radiating to the shoulders, fever, and distension had developed and increased, accompanied by nausea and vomiting. No evidence of shock had appeared. On admission, the clinical and roentgenologic findings were typical of a large right subdiaphragmatic collection of fluid, and 700 cc. of clear bile were obtained on surgical drainage. Convalescence was stormy but the drainage gradually lessened, and complete recovery followed. In this case it was impossible to demonstrate the site of the biliary perforation.

Case 6.—A female, age 68, was admitted to the University Hospital, 48 hours after the onset of severe upper abdominal pain, distension, and collapse. When first seen, the patient was *in extremis*, with marked cyanosis, and pronounced shock. A diagnosis of coronary thrombosis was made. The patient expired two hours after hospitalization. Postmortem examination disclosed 1,000 cc. of free bile in the peritoneal cavity; a gangrenous gallbladder and stones both in this structure and in the common duct. Careful study of the entire biliary tract disclosed no obvious site of perforation. *Pathologic Diagnoses:* Bile peritonitis; gangrenous cholecystitis; and paralytic ileus.

Case 7.—A female, age 60, was admitted to the University Hospital, with a history of eight years of chronic calculous cholecystitis, with one occurrence of jaundice. The patient was extremely obese, with a marked hypertension. Cholecystectomy with drainage, carried out under spinal anesthesia, revealed a hydrops of the gallbladder and a stone impacted in the cystic duct. The common duct appeared normal and was not explored. The patient went into shock on the table, and remained so for 24 hours. The temperature, pulse, and respirations then began to mount, with attendant signs of cardiac failure. Profuse drainage of bile was noted escaping along the abdominal drain, which continued until the patient expired 48 hours postoperative. Postmortem examination disclosed 200 cc. of bile in the right subdiaphragmatic space and right colic sulcus. A definite perforation of the cystic duct stump, proximal to the site of ligation, was found. The common duct was dilated but no stones were demonstrable. *Pathologic Diagnoses:* Perforation of cystic duct stump; bile peritonitis; pulmonary edema; and atelectasis.

Case 8.—A female, age 60, was admitted to the University Hospital, with a history of long standing chronic calculous cholecystitis, with intermittent common duct obstruction. Cholecystectomy and choledochostomy were performed, and stones were found in both the gallbladder and common duct. Recovery was uneventful, and a cholecystogram taken on the twelfth postoperative day, before removal of the T-tube, showed the common duct patent and well visualized. The patient was dismissed on the sixteenth postoperative day.

Twelve days later, she was readmitted with a history of two days of severe epigastric pain, gradually moving to the lower abdomen. Examination showed the patient to be acutely ill, with severe crampy abdominal pain, marked distension, definite clinical jaundice, and clay-colored stools. Vomiting was not a feature. Temperature 102° F.; pulse 120. Exploration revealed a diffuse bile peritonitis but demonstrated no definite site of perforation. Drains were introduced down to the region of the common duct. The patient expired 48 hours postoperative. *Postmortem:* Diffuse bile peritonitis; stone impacted in ampulla of Vater; moderate dilatation of common duct; perforation of stump of cystic duct; partial intestinal obstruction; and bronchopneumonia.

Etiology.—Bile has a strong natural tendency after its formation in the liver to follow its natural course down through the hepatic and common ducts and pass into the duodenum, provided there is no obstruction at the sphincter of Oddi. This same tendency continues even though an abnormal opening may occur in the duct wall above the sphincter.

Cope[1] has suggested as three factors which normally tend to prevent any extensive extravasation of bile: (1) The low pressure of biliary secretion and possibly its intermittency; (2) the natural tendency to closure of any abnormal opening; and (3) the readiness with which nature closes an opening in the extrahepatic ducts, even more striking than with other muscular tubes in the body.

A review of the subject of biliary peritonitis, however, discloses a variety of ways in which this condition may be produced:

(1) Biliary peritonitis without gross evidence of perforation:
  (a) Idiopathic leakage.
  (b) Microscopic perforation.
    1. Through gallbladder.
    2. Through extrahepatic ducts.
    3. Through intrahepatic ducts, with capsular rupture.
(2) Bile peritonitis following trauma:
  (a) Trauma to the abdomen:
    1. Rupture of the common duct.
    2. Rupture of the gallbladder.
    3. Rupture of the liver.
  (b) Leakage from the gallbladder bed following cholecystectomy.
  (c) Absorption or slipping of a cystic duct ligature.
  (d) Increased pressure in the biliary tree following cholecystectomy from overlooked common duct stone:
    1. Ruptured stump of cystic duct.
    2. Ruptured common duct.
    3. Rupture of intrahepatic duct.

(3) Bile peritonitis resulting from infection:
  (a) Perforation of the gallbladder.
  (b) Perforation of common duct.
  (c) Perforation of subserous duct in liver.
(4) Bile peritonitis secondary to increased intraductal pressure and perforation from unusual causes:
  (a) Stricture of duct.
  (b) New growth occluding ducts.
  (c) Congenital cystic dilatation of common duct.

A large number of cases of bile peritonitis without demonstrable perforation of the biliary tract have been reported in the continental literature during the past 40 years. Filtration of bile through the walls of the gallbladder or extrahepatic ducts was suggested as a route of spread, as was filtration through channels of Luschka's glands. Careful study of these cases, however, began to show that a small perforation, often microscopic in size, could be demonstrated in the majority of instances. These perforations often could only be identified by serial section at the site; because of their small size they would leak only when the intraductal pressure was increased, but would be quickly covered over as the pressure was relieved. A ruptured subserous bile duct on the liver surface was found to be one of the most frequent sites for these microscopic perforations. Schlaepfer,[2] after collecting 15 instances of this type from the literature, concluded that almost invariably a chronic cholangitis was present, with the perforation resulting from a sudden increase in intra-abdominal pressure. Cope[1] reported six personal cases of diffuse bile peritonitis without obvious perforation, and concluded that the most logical explanation was a small localized infection or ulceration in the mucosa of the biliary tree, with resultant microscopic perforation. Pohlman[3] stated that experimental work does not establish the existence of true biliary peritonitis in man without demonstrable perforation, although the perforation may be very difficult to find.

Bile peritonitis from a traumatic rupture of the gallbladder or common duct has been reported but is rare in the absence of preexisting disease in these structures. Traumatic rupture of the liver permits the escape of some bile but this feature is usually greatly overshadowed by the associated hemorrhage.

The presence of accessory hepatic ducts entering the gallbladder directly from the liver bed has often been observed. Mentzer[4] found these accessory hepatic ducts present in eight of 96 consecutive autopsies. They may easily be confused with collapsed veins during the performance of a cholecystectomy under ether anesthesia, which reduces the flow of bile. Probably these accessory hepatic ducts often account for the leakage of varying amounts of bile following cholecystectomy. Fear of such biliary leakage has been the principal reason for adherence to the principle of instituting drainage following all types of biliary surgery. Saunders,[5] Abell and Abell,[6] Wolfer,[7] and Graham,[8] have all reported series of cholecystectomies closed without drainage,

with gratifying results. None reported any fatalities from bile peritonitis, although Graham observed two instances of bile leakage after cholecystectomy, with subsequent recovery. Many other experienced surgeons feel that accessory hepatic ducts are a real hazard following cholecystectomy and insist upon routine drainage.

Diffuse extravasation of bile, resultant from premature absorption or slipping of the cystic duct ligature following cholecystectomy, undoubtedly occurs. If drainage has provided an avenue of escape for the bile, recovery may result without interference. Wolfer has demonstrated that a ligated cystic duct undergoes necrosis at the site of ligation, and closure of the duct end is dependent upon a proliferation of the adjacent tissue. These facts would suggest the advisability of covering over the ligated cystic duct stump with the adjacent peritoneum and not permitting the end of the drain to be in immediate contact with this site.

Overlooked common duct stones, with subsequent increased pressure in the biliary tree following cholecystectomy, may be followed by bile peritonitis, resultant from perforation of the biliary tree. The site of perforation may be through the ligated stump of the cystic duct, through the common duct, especially if this structure was opened at operation, or through a dilated intrahepatic bile radical on the hepatic surface. Wolfson and Levine[9] reported three cases of diffuse bile peritonitis developing between the thirty-fifth and forty-second days after cholecystectomy and choledochostomy. Two of these patients recovered following drainage of the common duct area while the third, at autopsy, showed a definite perforation at the site of the previous common duct incision with several stones in the lower portion of this duct. These authors attributed perforation to a localized infectious process in the wall of the common duct at the previous operative site.

Infection, whether acting alone or associated with external or surgical trauma, undoubtedly plays a major rôle in many cases of bile peritonitis. The association of cholangitis and hepatitis with cholecystitis is now a well-established and accepted fact. Smith[10] has reviewed 12 fatal cases of bile peritonitis from ruptured intrahepatic ducts. All these patients, 80 per cent female, were in the latter half of life, and all gave a long history of typical biliary colic, with intermittent common duct obstruction. In each instance, it was concluded that a chronic inflammatory process associated with gallstones had existed in the biliary channels for years. An exacerbation of the inflammatory process affected a group of the bile ducts in a small scar beneath the liver surface, with resultant necrosis of the overlying tissue, rupture, and peritonitis. Schlaepfer[2] came to similar conclusions in a study of his cases of intrahepatic rupture.

Perforation of the inflamed gallbladder very rarely results in the production of diffuse bile peritonitis. One of our seven cases developed incident to a gangrenous gallbladder, with associated common duct stones, but no definite site of perforation was demonstrable at autopsy. Several years ago, the author, with E. L. Eliason,[11] found, in a review of this subject, that while the incidence of perforation of the gallbladder varied from one to three per

cent in the reported series of biliary admissions, few of these cases showed evidence of biliary peritonitis. In a series of 490 consecutive biliary admissions, perforation of the gallbladder had occurred in nine cases, but diffuse bile peritonitis was not found in a single instance; undoubtedly due to the fact that the perforating gallbladder tends to be well walled-off by adjacent structures before actual perforation occurs.

That strictures and new growths occluding the biliary ducts may contribute to perforation and biliary peritonitis is quite evident. These conditions readily produce the element of obstruction and, with associated infection, set the stage for perforation. Caulfield[12] reported two cases of bile peritonitis occurring in infants during the first month of life, with one recovery. In the fatal case, a stricture of the lower common duct was found and the bile escaping through a perforation above this was localized in a serous lined sac in the upper abdomen. It was suggested that this picture might represent the first stage of the so-called idiopathic dilatation of the common duct seen in older children.

Our observations lead us to believe that increased pressure within the biliary tree from overlooked common duct stones is the most frequent basic factor in the production of biliary peritonitis. The presence of such stones in three of our five fatal cases supports this conclusion.

Pathology.—The seriousness of an extensive extravasation of free bile within the peritoneal cavity has been the subject of a great deal of controversy. Some insist that free, uncontaminated bile within the peritoneal cavity is never lethal, and others consider death inevitable if sufficient bile escapes and is not drained. The considerable number of fatal cases following perforation of the biliary tree would seem to refute the statement that bile peritonitis is never fatal, and yet patients are observed who, for long periods, have harbored extensive intraperitoneal collections of bile without being seriously ill.

It is very important to differentiate accurately between bile peritonitis and ascites, since these conditions may be confused. Ravdin, *et al.*,[13] have shown that true biliary peritonitis demands the presence of free bile in the peritoneal cavity with a corresponding peritoneal irritation, while biliary ascites appears in cases of common duct obstruction with portal stasis in which efforts at setting up a collateral circulation are only partially adequate. In this latter condition, the resultant ascites is bile-stained from the general icterus and the bile salts present come from the blood bile salts rather than a filtration or perforation through the hepatic duct walls.

In an effort to better understand the effect of free bile within the peritoneal cavity, numerous experimental studies have been undertaken in recent years,[14, 15, 16, 17, 18, 19, 20] the majority of which have been made on dogs. Many of the published results conflict and do not correspond to clinical cases observed. Mentzer[21] has pointed out that bile peritonitis in the dog is not comparable to that seen in man, since the bile of the dog is approximately 40 times as lethal when extravasated intraperitoneally as is human bile.

The experimental studies, published to date, suggest that free bile in the peritoneal cavity produces its serious effects through one or a combination of several of the following ways:

(1) Toxic action of one or more of the products present in bile upon tissues.
(2) Infection carried into the peritoneal cavity by the bile or subsequently developing through contamination.
(3) Production of a condition simulating surgical shock through the outpouring of large amounts of plasma-like fluid into the abdomen from the blood stream, associated hemoconcentration, lowered blood volume, and fall in blood pressure.

The former concept that bile peritonitis produced death through toxic action of the bile salts and bile acids is supported by few investigators to-day. It is probable that the action of the bile salts upon the peritoneum makes this structure less resistant to infection. Mentzer,[21] Rewbridge,[22] and Weinberg and Levenson,[23] all consider that pathogenic bacteria passing through a peritoneal barrier damaged by the action of the bile salts are the primary cause of the fatal outcome in these cases. In clinical practice, it is unusual in a patient who has survived for any period of time to find bile which has not become infected. The usual organisms found are the streptococci, colon bacilli, and certain of the anaerobes.

In 1931, Ziegler and Orr[17] observed that the peritoneal cavities of experimental animals with bile peritonitis at autopsy were filled to the point of distension with bile-stained fluid. Subsequently, Harkins, *et al.*,[18, 19, 20] Moon and Morgan,[15] and Manson and Eginton,[16] published data demonstrating the presence of a secondary surgical shock syndrome in their animals with bile peritonitis. The extravasated bile, or its salts, injured the walls of the capillaries and venules, with resultant atony, increased permeability, and produced a tremendous outpouring of plasma from the blood into the peritoneal cavity. There resulted a concentration of the hemoglobin, fall in blood pressure, and clinical evidence of shock. This syndrome, sufficient alone to cause death in many instances, even if not lethal, so alters normal resistance that the subject is unable to resist bacteria or toxic factors which normally would not prove fatal.

Clinical Picture.—It seems probable that this same shock-like picture seen in experimental animals occurs in variable degrees in clinical cases. Three of our cases of bile peritonitis demonstrated definite evidence of shock, and tachycardia was a striking clinical feature. Biliary peritonitis should, therefore, be suspected in any patient who has recently been operated upon for biliary disease and whose subsequent appearance suggests delayed surgical shock. One's suspicions are naturally confirmed if bile is found escaping along the abdominal drain in considerable amounts, as happened in four of our cases.

Bile peritonitis developing without previous biliary surgery is rarely diag-

nosed before an exploratory celiotomy. Power[24] observed that early cases simulate a perforated peptic ulcer, although the picture does not seem so acute. When the patient is seen later, ruptured appendicitis, general peritonitis, pancreatitis, or intestinal obstruction may be suspected. These patients may even simulate cardiac emergencies, as one of our cases, admitted *in extremis*, was considered to be a coronary thrombosis until autopsy disclosed the true nature of the lesion. Exploration, and finding of free bile in the peritoneal cavity, make the diagnosis, although in many instances the exact site of perforation cannot be demonstrated.

Treatment.—The successful treatment of bile peritonitis demands adequate drainage as soon as the condition is recognized. Ideally, the perforation should be closed in addition to abdominal drainage, but rarely is one able accurately to identify this site, since the patient's condition usually demands rapid exploration, with a minimum amount of manipulation. All free bile should be removed by suction, and the pelvis and subdiaphragmatic areas emptied as completely as possible. Drains are placed down to the region of the common duct; occasionally it is of value to drain the pelvis.

Postoperatively, every effort should be directed toward support of the patient. The large quantities of fluid lost should be replaced by parenteral routes and a transfusion is of great value. Blood plasma, if available, should replace that which has passed into the peritoneal cavity from the blood stream. Administration of adequate fluid will overcome the hemoconcentration and relieve the shock-like features of the condition.

Mortality.—Diffuse biliary peritonitis is an extremely serious complication following biliary surgery, and results in a high mortality rate. Cope reported a mortality of 66 per cent in his six cases; our mortality was 62 per cent. The fulminating cases tend to expire in a very short period of time, in spite of all treatment, while infection is a major hazard in those in whom the process develops more slowly. All hope of improving the results in this series of patients would seem to lie in suspecting this complication when certain of its symptoms and signs are present; and the institution of immediate drainage.

SUMMARY AND CONCLUSIONS

(1) The problem of diffuse and localized bile peritonitis is discussed together with a presentation of eight cases.

(2) An outline of the various ways in which this complication may arise is presented together with a discussion of the resultant pathology.

(3) The mortality is high, ranging from 50 to 75 per cent in the reported clinical cases. The mortality in our series was 62 per cent.

(4) Treatment demands exploration as soon as the condition is suspected, with surgical drainage and energetic postoperative therapy.

REFERENCES

[1] Cope, Z.: Extravasation of Bile. Brit. Jour. Surg., **13**, 120–129, 1925.

[2] Schlaepfer, K.: The Etiology of Bile Peritonitis. J. of Int. Coll. of Surg., **2**, 427–433, 1939.

[3] Pohlman, H. F.: Biliary Peritonitis without Perforation as a Clinical Entity. Am. J. Surg., **46**, 400–401, 1939.
[4] Mentzer, J. H.: Anomalous Bile Ducts in Man. J.A.M.A., **93**, 1273–1277, 1929.
[5] Saunders, R. L.: Discussion—Anomalous Bile Ducts in Man. J.A.M.A., **93**, 1277, 1929.
[6] Abell, I., and Abell, I., Jr.: The Question of Drainage Following Cholecystectomy. ANNALS OF SURGERY, **112**, 1035-1042, 1940.
[7] Wolfer, J. A.: Bile Leakage from Cystic Duct Following Cholecystectomy: Experimental Study of Obliteration of Cystic Duct Stump. Surg., Gynec., and Obstet., **49**, 462–472, 1929.
[8] Graham, H.: Discussion—Drainage Following Cholecystectomy. ANNALS OF SURGERY, **112**, 1040, 1940.
[9] Wolfson, W. L., and Levine, D. R.: Spontaneous Rupture of the Common Duct: Sequelae of Choledochostomy. Surg., Gynec., and Obstet., **60**, 746–747, 1935.
[10] Smith, W.: Rupture of an Intrahepatic Duct, with Fatal Peritonitis. ANNALS OF SURGERY, **83**, 55–68, 1926.
[11] Eliason, E. L., and McLaughlin, Charles W., Jr.: Perforation of the Gallbladder. ANNALS OF SURGERY, **99**, 914-922, 1934.
[12] Caulfield, E.: Bile Peritonitis in Infancy. Am. J. Dis. Children, **52**, 1348–1360, 1936.
[13] Ravdin, I. S., Morrison, M. E., and Smythe, C. M., Jr.: Bile Peritonitis and Bile Ascites. ANNALS OF SURGERY, **89**, 867-878, 1929.
[14] Horrall, O. H.: Experimental Bile Peritonitis and Its Treatment in the Dog. Arch. Int. Med., **43**, 114–129, 1929.
[15] Moon, V. H., and Morgan, D. R.: Shock in Bile Peritonitis. Proc. Soc. Exp. Biol. Med., **34**, 743–748, 1936.
[16] Manson, M. H., and Eginton, C. T.: The Cause of Death in Bile Peritonitis. Surgery, **4**, 392–404, 1938.
[17] Ziegler, A. M., and Orr, T. G.: Clinical Changes in the Blood of the Dog in Experimental Bile Peritonitis. Jour. Exp. Med., **53**, 865–868, 1931.
[18] Harkins, H. N., Harmon, P. H., Hudson, J., and Andrews, E.: Mechanism of Death in Bile Peritonitis. Proc. Soc. Exp. Biol. and Med., **32**, 691–693, 1935.
[19] Harkins, H. N., Harmon, P. H., and Hudson, J. E.: Lethal Factors in Bile Peritonitis. Arch. Surg., **33**, 576–609, 1936.
[20] Harkins, H. N., Harmon, P. H., and Hudson, J. E.: Peritonitis Due to Bile and to Liver Autolysis. J.A.M.A., **107**, 948–953, 1936.
[21] Mentzer, S. H.: Bile Peritonitis. Arch. Surg., **29**, 227–241, 1934.
[22] Rewbridge: Arch. Surg., **29**, 227–241, 1934. Quoted by Mentzer.[4]
[23] Weinberg and Levenson: Peritonitis—Collective Review. Int. Abst. Surg., **67**, 339–355, 1938. Quoted by Harvey, H. D., and Meleney, F. L.
[24] Power, S.: Biliary Peritonitis. Brit. Med. Jour., **2**, 948–949, 1935.

BLACK WIDOW SPIDER BITE

H. T. KIRBY-SMITH, M.D.

SEWANEE, TENN.

FROM THE EMERALD-HODGSON HOSPITAL

THE EFFECT of the bite of *Latrodectus Mactans*, or Black Widow spider, is not in itself a surgical problem. However arachnidism is occasionally mistaken for an acute abdominal condition requiring immediate operation, a mistake comprehensible in view of the extreme severity of abdominal pain following Black Widow spider bites, the difficulty of obtaining an adequate history after the onset of severe symptoms, and the frequent failure of the victim to attach importance to the comparatively slight sting of the actual bite or to associate it with the excruciating abdominal cramping which begins shortly afterwards.

The Black Widow spider bite and its symptoms have been known to some extent for many years,[2, 16] but only within the last 14 years has the frequency of the condition been recognized and reported. During this period a number of articles dealing with the subject of arachnidism have appeared in various medical periodicals but only twice have surgical journals published reports on the subject.[37, 38] Because the Black Widow spider bite is far more frequent than was formerly supposed and because its symptoms simulate an acute abdominal condition, the following discussion is offered.

In the series of 24 cases herewith tabulated, 15 were collected from the records of Vanderbilt Hospital, Nashville, Tenn., from 1925 to 1939, and nine cases were seen by the writer during five years of private practice from 1935 to 1940. An examination of the case reports will reveal the following salient facts.

No cases were reported prior to 1933, and since that time the number seen and reported each year are as follows:

1933-1; 1934-1; 1935-2; 1936-4; 1937-7; 1938-5; 1939-1; 1940-3.

In 14 of the 24 cases the Black Widow itself was actually seen. In the other ten cases the history and subsequent course of symptoms leave no doubt that they were clear and authentic cases of Black Widow spider bites.

The location of the bites is of interest. Eleven were bitten on the penis, four on the buttocks, one on the scrotum, one on the thigh, four on the arms and hands, one on the chest, one on the knee, and in one case the site was not mentioned. Sixteen of the victims were bitten while in a privy, two inside a house, two on a porch, and only four out of doors.

The bites occurred during the hours of darkness in 13 cases, during the daytime in nine cases and no mention is made of the time in the other two cases.

There is no significance in age-grouping, there being one patient 14 months old, and one 78 years old, with a scattering of different ages between the two.

It is interesting to note that 22 of the cases were males, there being only two females bitten.

The onset of symptoms varied from five minutes to two and one-half hours following the bite. In the majority of the cases severe pain was felt within 30 minutes. As a rule, pain continued for a considerable period of time. The time of disappearance of pain was reported in 20 cases, the duration of time varying from one to three days. The average duration of pain was 24 hours.

The time of year seems to be closely related to the number of cases seen. In this series of cases the season extends from April through October. The following are the figures for the number bitten each month:
April-2; May-3; June-5; July-1; August-5; Sept.-3; October-5.

One patient was bitten twice, both times on the penis while in an outdoor privy. There was an interval of 41 days between the two bites. The symptoms following the second bite were less severe than those which succeeded the first. This fact is probably attributable to the amount of venom injected rather than to an acquired immunity as, according to D'Amour, immunity is acquired slowly and after repeated injections of the venom.

In the series reviewed, one fatality occurred, and one case in which mistaken diagnosis led to celiotomy. Both of these cases are herewith reported:

Case 1.—*Fatality:* Hosp. No. 15034: W. D., white, male, age 69, was admitted to Vanderbilt Hospital at 1:00 P.M., June 28, 1937. He had been treated in the Out-Patient Clinic intermittently since June, 1935, for hypertension, arteriosclerosis, duodenal ulcer, and arthritis of the lumbar spine. He had been feeling quite well until seven and one-half hours before admission. At that time he had been bitten on the scrotum by a "small black spider" while he was sitting in a privy. About 15 minutes after having been bitten he had a stinging sensation on the scrotum which was followed by severe deep pains in the upper thighs. The pain spread downward to the knees and up into the abdomen to the level of the umbilicus. He consulted a physician and one-half hour before admission to the hospital was given gr. 1/16 dilaudid, and gr. 1/150 atropine.

Examination revealed a fairly obese, elderly man, lying rather quietly in bed, complaining of pain in the lower abdomen, genitalia, lower back and upper thighs. The important physical findings were tortuosity of the retinal vessels, thickening and tortuosity of the peripheral arteries, blood pressure 194/86, and a small red pinpoint area on the scrotum, presumably where the bite had occurred. The abdomen was only moderately rigid, with some tenderness in the lower quadrants. R.B.C. 4,680,000; W.B.C. 10,000; hemoglobin 14 gm.; differential count normal. Pulse 80, temperature normal.

Shortly after admission the patient was given 10 cc. of 10 per cent solution calcium gluconate intravenously, without appreciable relief being afforded. The only relief obtained was from hot baths, and this was temporary. At 7:00 P.M. 2 cc. of 50 per cent magnesium sulphate was given intramuscularly. At 8:00 P.M. 1/6 gr. morphine was given. At 9:30 P.M. 20 cc. of calcium gluconate was administered intravenously and 1/4 gr. morphine was given at the same time. At 11:00 P.M. 2 cc. of 50 per cent magnesium sulphate was given intravenously and 1/4 gr. morphine given subcutaneously. All this medication afforded very little relief. The patient became cyanotic and, in spite of the administering of caffeine sodium benzoate and adrenalin, he died at 1:40 A.M. the following morning. At no time was there any indication of cardiac enlargement or pulmonary edema. An autopsy was not granted.

The following is a brief case report of a patient upon whom a celiotomy was performed following a mistaken diagnosis.

TABLE I

BLACK WIDOW SPIDER BITES

Age	Sex	Location of Bite	Place When Bitten	Time	Appearance of Symptoms	Symptoms and Signs	Treatment	Duration of Symptoms
8	M.	Chest	House	6:50	15 minutes	Cramping in legs and abdomen. Abdomen tense.	Morphine. Calcium gluconate	30 hours
68	M.	Penis	Privy	3:00 P.M.	Few minutes	Cramping in abdomen, chest and back. Abdomen tense.	Acetylsalicylic acid	12 hours
11	M.	Knee and groin	?	4:00 P.M.	2 hours	Cramping in legs, abdomen, chest and back. Abdomen tense.	Codeine. Sodium phenobarbital. Hot bath. $MgSO_4$ intramuscularly	24 hours
14 mos.	F.	Thumb	Porch	?	5 minutes	Restless and vomiting. Abdomen tense.	$MgSO_4$ intramuscularly	24 hours
13	M.	Buttocks	Privy	8:30 P.M.	15 minutes	Pains in back and abdomen. Abdomen tense.	Calcium gluconate. Morphine. Atropin	12 hours
16	M.	Buttocks	Privy	Night	2 hours	Pains in back and chest. Abdomen examination not mentioned.	$MgSO_4$ intramuscularly	12 hours
26	M.	Hand	Out of doors	Day	Not mentioned	Pains in wrist, arms, shoulders, and abdomen. Drunk on admission.	Morphine	?
17	M.	Penis	Privy	11:00 P.M.	1–2 hours	Generalized aching. Seen five days after bite.	"Pills"	?
17	M.	Penis	Privy	6:45 P.M.	10 minutes	Cramping in abdomen, aching in back. Abdomen tense.	Calcium gluconate	24 hours
40	M.	?	Privy	Night	1 hour	Cramping in abdomen, back, neck. Abdomen tense.	Celiotomy	?
15	M.	Buttocks	Privy	?	1 hour	Pains in knees, hips, and chest. Abdomen soft.	Morphine	24 hours
69	M.	Scrotum	Privy	5:30 A.M.	30 minutes	Pains in thighs and abdomen. Abdomen tense.	Dilaudid. Atropin. Calcium gluconate. $MgSO_4$ intravenously. $MgSO_4$ intramuscularly	Died
18	M.	Buttocks	Privy	1:00 P.M.	Few minutes	Pains in groins, back, and abdomen. Abdomen tense.	$MgSO_4$ intramuscularly	12 hours
35	M.	Penis	Privy	Night	Few minutes	Pains in thighs, abdomen, back, legs, shoulders, and neck. Abdomen tense.	Calcium gluconate. Hot baths. Morphine	24 hours
15	M.	Arm	Field	10:30 A.M.	1½ hours	Pains in arm, back, abdomen, and thighs. Abdomen tense.	Hot baths. Codeine	24 hours
37	M.	Penis	Privy	6:00 P.M.	15 minutes	Aching in lower abdomen. Abdomen soft.	$MgSO_4$ intramuscularly	24 hours
35	M.	Penis	Privy	8:00 A.M.	10 minutes	Pains in thighs, abdomen, and back. Abdomen tense.	Morphine. Dilaudid. Calcium gluconate. Hot baths	3 days
4	F.	Thumb	Out of doors	5:00 P.M.	Few minutes	Restless and crying. Abdomen tense.	One ampoule antivenin	1 hour
16	M.	Thigh	Bed	3:00 P.M.	½ hour	Pains in abdomen, back, and neck. Abdomen tense.	Morphine	24 hours
37	M.	Penis	Privy	6:00 P.M.	15 minutes	Aching in lower abdomen. Abdomen soft.	$MgSO_4$ intramuscularly	24 hours
66	M.	Penis	Privy	8:00 P.M.	30 minutes	Cramping in abdomen, chest, and back. Abdomen tense.	Morphine. Amytal	12 hours
78	M.	Penis	Privy	9:30 P.M.	30 minutes	Cramping in abdomen and back. Abdomen tense.	Morphine	3 days
78	M.	Penis	Privy	8:45 P.M.	2½ hours	Pains in thighs, hips, abdomen, and chest. Abdomen tense.	Calcium gluconate	12 hours
21	M.	Penis	Privy	8:30 P.M.	15 minutes	Cramping in abdomen and chest. Abdomen tense.	Morphine. Calcium gluconate. Hot baths	16 hours
36	M.	Penis	Privy	9:00 P.M.	Approximately 1 hour	Cramping in abdomen, thighs, back, and arms. Abdomen soft.	None. Seen 14 hours after bite	24 hours

Volume 115
Number 2

Case 2.—Hosp. No. 80568: H. J., white, male, age 40, was admitted to Vanderbilt Hospital, August 28, 1936, complaining of severe abdominal pain of three hours' duration. The attack began with a cramping in the abdomen necessitating a bowel action and, after returning from the out-door privy, the pain became much worse. In an hour he was suffering severely. Because of this he came to the hospital and was admitted three hours after the onset of pain. Further questioning revealed the fact that four years previously he had had an attack of abdominal pain associated with hematemesis and was told that he had a stomach ulcer.

Examination on admission showed a middle-aged white male in severe pain, in fact, so severe that a careful history was hard to obtain. He was complaining of pain in the abdomen, back, and neck. The significant physical finding was limited to the abdomen which was board-like. The pulse and respirations were increased; temperature normal; W.B.C. 6,900; urine negative. A roentgenogram of the abdomen, in an upright position, showed no air under the diaphragm. *Preoperative Diagnosis:* Ruptured peptic ulcer. The abdomen was opened and nothing of significance was found.

The following day, when the patient was more comfortable, a careful history revealed the fact that he remembered having been bitten while in the privy and having seen a black spider. He did not think of attributing his abdominal pain to this cause. His recovery following the operation was uneventful and he was discharged from the hospital after nine days.

The Spider.—The Black Widow spider, or *Latrodectus Mactans*, has been found in all the states of the United States with the exception of Vermont and in Canada. It is frequently found near human habitations but also lives in woods and fields. It has a preference for protected places. In the writer's experience, specimens have been easily found in basements and out-buildings, under boards and rocks and in cans and pipes. As a rule, the spiders are not found in large numbers in old buildings where the basements and corners are filled with old webs but they are easily discovered in new, clean basements.

The Black Widow is a common spider. During the summer of 1938 the writer killed more than 20 in and around his house in Winchester, Tenn. During the summer of 1937 a neighbor found more than 80 spiders in his house or adjacent out-buildings. D'Amour and his associates[18] collected 6,500 specimens in the course of one summer while studying the effects of Black Widow venom. In a letter received recently from Sharp and Dohme, of Philadelphia, in reply to an inquiry regarding the manufacture of antivenin *Latrodectus Mactans* the following statement was made: "We have experienced no difficulty in obtaining Black Widow spiders. During the summer months they occur abundantly in low lying fields on the coastal plains of the Middle Atlantic States."

In view of the tremendous number and wide distribution of these spiders it would seem that surprisingly few persons are bitten. The explanation is apparent if the actions of the spider are observed. When the web of a Black Widow is disturbed she retreats with rapidity and even when cornered she seldom makes a show of resistance or offers to bite. Ordinarily, a human being is bitten only when the spider is crushed against the body or when the web is disturbed in the dark or under some other condition which causes the spider to mistake the disturbing object for its usual prey. Sometimes a person is bitten in bed, presumably when he mashes the spider. Occasionally

one is bitten when lifting boards or rocks. More frequently bites occur when the web is disturbed in the dark as indicated by the large number of patients bitten at night in privies when the web is agitated and the spider attacks without seeing what object has been entangled.

The Black Widow is easily identified. It is the female of the species that is poisonous and there is no other spider that is at all similar in appearance. The mature female is solid black and has a large spherical abdomen and long, strong-looking legs. On the ventral surface of the abdomen is a bright red hour-glass marking. The adult male has legs of the same type but a much smaller body. Its markings are quite different, there being white, orange and brown bands and spots on its body and contrasting light and dark bands on its legs. The smaller, immature females have a row of red dots on the dorsal surface in addition to the red hour-glass marking on the ventral side. When first hatched the male and female are identical in appearance but as moulting progresses they assume their respective characteristics.

The web of the Black Widow is easily identified. It has no regular pattern. Its threads are coarse and irregularly spaced. There is no well-developed funnel hiding area.

A complete discussion of the characteristics and life history of the Black Widow spider can be found in a publication by D'Amour and his associates,[18] and also in an article by Blair.[10]

The Black Widow is armed with a pair of hollow fangs connected to a pair of poison glands. The latter are located in the cephalothorax just behind the eyes. Microscopically, they are composed of a basement secreting layer of cells with a surrounding layer of muscle.[18] The latter structure is considered to be important and it is thought that the muscle layer is subject to the active control of the spider, the amount of venom injected being thus regulated.

Studies by D'Amour and his associates show that the average adult female spider carries venom in its poison sacs which, when dried, produces 0.064 mg. of solid residue. One-fourth of this amount of venom when dissolved and injected into young rats will kill about half the number treated. The venom retains its potency when dried but deteriorates rapidly in solution. Using mortality statistics, they conclude that, weight for weight, Black Widow venom is 15 times as toxic as the venom of the rattlesnake.

Symptoms and Treatment of Black Widow Bites.—The course of symptoms following the bite of a Black Widow spider is striking. Usually the victim is in extreme pain when first seen, and is unable to remain still long enough to be examined properly. The greatest pain is centered in the abdomen with some involvement in the back, hips and lower chest. The pain usually begins in the muscle groups nearest the site of the bite and spreads toward the abdomen. If the bite is on the hand, the forearm, upper arm, shoulder, chest and abdomen are successively involved. If the bite is on the genitalia, as is frequently the case, the pain is in the hips and thighs first, spreading later to the back, abdomen and lower chest.

In a typical case the patient gives a history of having felt a bite or sting,

like the sting of a wasp or the prick of a splinter. The bite may be ignored and recalled only when the patient is questioned directly. Usually within 30 minutes, sometimes after a longer period, the victim begins to have a dull cramping in the muscle group nearest the site of the bite. By the time the pain has spread into the abdomen, back and lower chest, it is very severe and equals or exceeds that of ruptured peptic ulcer, kidney colic, acute appendicitis or coronary occlusion.

Examination reveals obvious pain. The abdomen is board-like but moves with respiration. Later, pulse and respirations are somewhat increased. Temperature is usually normal during the first few hours but may become slightly elevated later. There may be nausea or vomiting but these symptoms do not necessarily appear.

The bite usually produces no local signs or symptoms but sometimes the fang marks can be seen—small red dots and, in delicate tissues such as the penis, a very small area of local edema is seen.

The various laboratory procedures do not aid materially in the diagnosis. There is apt to be a moderate leukocytosis but this is not constant. The red blood count, hemoglobin, differential and urine examination show no significant changes. The spinal fluid pressure may be elevated but is normal as to cellular elements.

Morphine is usually given. It affords little relief and is usually repeated. Other types of treatment are described below. After several hours the pain is somewhat abated but may recur in milder character for as long as two or three days.

Because of the severity of the pain it is sometimes difficult to obtain a satisfactory history. If the possibility of spider bite is not considered, a mistaken diagnosis of an acute abdominal condition may be made.

A great many types of treatment have been suggested for relieving the symptoms of Black Widow spider bites. Of these none offers consistent relief. Morphine and the opium derivatives help only to a small extent. The barbiturates are not effective. Magnesium sulphate given intravenously in 10 per cent solution and intramuscularly in 25 per cent solution is said to be of considerable benefit. Calcium gluconate given intravenously in dosages of 10 cc. of 10 per cent solution is effective to some extent in relieving pain. Lumbar puncture has been suggested as a method of affording some relief. In certain cases hot baths give a great deal of additional relief.

Serum therapy is in the experimental stage. Serum from patients who have been bitten has been used but it is of doubtful efficacy. D'Amour[18] found that in rats a serum could be made which, in one cubic centimeter doses, would protect them against four times the average lethal dose of spider venom. This immunity was built up quite slowly, and in rats 27 injections of venom were given over a period of ten weeks in order to produce a potent serum. There is a serum available commercially which is said to neutralize the venom from 750 spiders. This was used in treating one of the last two cases seen by the writer, the victim being, in this instance, a four-year-old

girl. The child was playing in the yard with a tin can in which there was a spider. She was bitten on the hand and in a few minutes began to complain. One hour after the bite she was seen in the hospital. She was in great pain and unable to lie quietly. On the thumb was a small reddish area which was said to be the site of the bite. The abdomen was rigid, the temperature normal, and the pulse elevated. The child's mother stated that the spider was black with a red spot on its abdomen. A single dose of the antivenin was given subcutaneously. No other medication was given. In an hour the patient was asleep and the abdomen soft. She was kept in the hospital two days for observation and there was no recurrence of pain. It will be interesting to note whether similar results are obtained by the use of this antivenin in the future.

End-Results.—Fatalities following Black Widow spider bites are quite uncommon notwithstanding reports by Bogen,[14] who collected approximately 600 cases of such bites with 40 recorded deaths. This would indicate a mortality rate of 6.6 per cent. The records of these deaths were not obtained from published articles but were collected from death certificates, newspaper reports and personal communications.

In 248 cases, collected from the literature (references 6, 9, 14, 16, 17, 20, 23, 24, 27, 28, 29, 33, 37, 39, 40, 41, 42, 44, 48, 50, 51, 55, 56) there were no recorded fatalities. Among them was Ginsberg who, in reporting 96 cases, remarked than none died and that none of them was seriously ill.

Although there have been deaths resulting from Black Widow spider bites, a review of the literature fails to reveal any deaths reported in detail.

Judging from the cases reviewed in the present series, it appears that arachnidism usually results in complete recovery without sequelae after a period of three days or less.

SUMMARY

(1) Twenty-four cases of Black Widow spider bites are analyzed as to age, sex, location of bite, place when bitten, appearance of symptoms, treatment, and duration of symptoms.

(2) Two cases are reported in detail, one being the only fatality occurring in the series and the other, a case in which mistaken diagnosis led to celiotomy.

(3) The spider, his distribution, habits and venom are discussed.

(4) The symptoms and treatment of Black Widow bites are discussed.

(5) End-results of Black Widow bites are discussed.

CONCLUSIONS

(1) The bite of *Latrodectus Mactans*, or Black Widow spider, is more common than was formerly supposed.

(2) Symptoms of Black Widow bite may simulate an acute surgical condition.

(3) Fatality resulting from the Black Widow spider bite is rare.

(4) No uniformly satisfactory treatment for the relief of symptoms has been found.

(5) The single case in which antivenin was used, and resulted in immediate relief, suggests the possibility that its further use may afford more adequate relief than has heretofore been obtained by other methods of treatment.

BIBLIOGRAPHY

[1] Abrams, M. J.: Arachnidism. Bulletin of the School of Medicine, University of Maryland, **18**, 92–97, 1934.

[2] Alexander, J.: Early Reference to Black Widow Spider. Science, **84**, 552–553, 1936.

[3] Allard, H. A.: Distribution of the Black Widow Spider. Science, **85**, 74–75, 1937.

[4] Allen, W. H.: The Black Widow Spider. Military Surgeon, **77**, 352–353, 1935.

[5] Anderson, L. D., and Walker, H. G.: Notes on the Distribution of the Black Widow Spider. Science, **85**, 100–101, 1927.

[6] Baerg, W. J.: The Effects of the Bite of Latrodectus Mactans. Jour. Parasitol., **9**, 161–169, 1922.

[7] Beazley, R. N.: Death From the Bite of a Trap-door Spider. Med. Jour. Australia, **31**, 265, 1930.

[8] Becker, F. E., and D'Amour, F. E.: Black Widow Spiders, A Warning. Colorado Med., **54**, 844–850, 1934.

[9] Blair, A. W.: Spider Poisoning. Arch. Int. Med., **54**, 831–843, 1934.

[10] Blair, A. W.: Life History of Latrodectus Mactans. Arch. Int. Med., **54**, 844–850, 1934.

[11] Bogen, E.: Arachnidism. J.A.M.A., **86**, 1894–1896, 1926.

[12] Bogen, E.: Arachnidism. Arch. Int. Med., **38**, 623–632, 1926.

[13] Bogen, E., and Berman, P.: Poisonous Spider Bites with Especial Reference to Latrodectus Mactans. Calif. and West. Med., **26**, 339–341, 1927.

[14] Bogen, E.: Poisonous Spider Bites. Ann. Int. Med., **6**, 375–378, 1932.

[15] Bogen, E., and Loomis, R. N.: Poisoning Poisonous Spiders. Calif. and West. Med., **45**, 31–37, 1936.

[16] Chapman, W. H.: Arachnidism, Spider Bite Poisoning. U.S. Veterans' Bureau Med. Bull., **12**, 241–245, 1936.

[17] Cornwell, A. M.: Arachnidism. South. Med. and Surg., **93**, 885–886, 1931.

[18] D'Amour, F. E., Becker, F. E., and Van Riper, W.: The Black Widow Spider. Quart. Rev. Biol., **11**, 123–160, 1936.

[19] D'Amour, F. E.: A Comparative Assay of Black Widow Antisera. Proc. Soc. Exper. Biol. and Med., **25**, 262–263, 1936.

[20] Ellie, J. B.: Arachnidism. Ann. Int. Med., **3**, 924–927, 1930.

[21] Frawley, J. M., and Ginsberg, H. M.: The Diagnosis and Treatment of Black Widow Spider Bites. J.A.M.A., **104**, 1790–1792, 1935.

[22] Gilbert, E. W., and Stewart, C. M.: Effective Treatment of Arachnidism by Calcium Salts. Amer. Jour. Med. Sci., **46**, 381–385, 1935.

[23] Ginsberg, H. M.: Black Widow Spider Bite. Calif. and West. Med., **46**, 381–385, 1937.

[24] Gray, R. M.: Black Widow Spider Poisoning. Calif. and West. Med., **43**, 328–331, 1935.

[25] Hagan, H.: Arachnidism. Kentucky Med. Jour., **36**, 120–121, 1938.

[26] Hall, W. W.: Spider Poisoning: A Study of the Toxin of the Black Widow Spider. United States Naval Med. Bull., **30**, 471–478, 1932.

[27] Hargis, A. S.: Arachnidism. New England Jour. Med., **215**, 489–492, 1936.

[28] Henderson, W. C.: Arachnidism on the Eastern Shore of Virginia. Virginia Med. Month., **61**, 605–606, 1935.

[29] Hodgdon, A. L.: Bite of a Poisonous Spider, Latrodectus Mactans. J.A.M.A., **48,** 1506, 1907.
[30] Irwing, W. G., and Hinman, E. H.: The Blue Mud-dauber as a Predator of the Black Widow Spider. Science, **82,** 395–396, 1935.
[31] Jellison, W. L., and Philip, C. B.: The Biology of the Black Widow Spider, Latrodectus Mactans. Science, **81,** 71–72, 1935.
[32] Kaston, B. J.: Distribution of Black Widow Spiders. Science, **85,** 74, 1937.
[33] Kirkwood, T.: Poisonous Spider Bites in Illinois; with Case Reports. Illinois Med. Jour., **67,** 377–379, 1935.
[34] Louis, D. J.: Black Widow Spider Poisoning. Illinois Med. Jour., **70,** 195–197, 1936.
[35] Louis, D. J.: Black Spider Poisoning. J.A.M.A., **76,** 99, 1921.
[36] Lourie, D. C.: New Localities for the Black Widow Spider. Science, **84,** 437, 1936.
[37] Morton, C. B.: Acute Abdominal Symptoms in Arachnidism. Arch. Surg., **26,** 64–71, 1933.
[38] Noland, L.: Arachnidism. Amer. Jour. Surg., **20,** 758–762, 1933.
[39] Palmer, H. E.: Spider Poisoning from the Bite of Latrodectus Mactans or Black Widow Spider. Jour. Florida Med. Assn., **17,** 64–69, 1930.
[40] Prey, D.: Arachnidism. Colorado Med., **27,** 440–442, 1930.
[41] Robinson, H. M., Jr.: A Case of Acute Urinary Retention Following the Bite of Black Widow Spider. Bulletin of the School of Medicine, University of Maryland, **22,** 117–120, 1938.
[42] Rohlfing, E. H., and Bullington, B. M.: Poisoning from the Bite of Black Widow Spider. Jour. Pediat., **7,** 79–80, 1935.
[43] Schmans, L. F.: Case of Arachnidism. J.A.M.A., **92,** 1265–1266, 1929.
[44] Shaw, H. L.: Report of Spider Bite. Jour. South Carolina Med. Assn., **32,** 155, 1936.
[45] Shield, J. A.: Arachnidism. South Med. and Surg., **99,** 278–279, 1937.
[46] Stiles, K. A.: The First Record of Black Widow Spider Bite for Iowa. Science, **85,** 334–335, 1937.
[47] Taylor, K. L.: The Black Widow Spider in Virginia. Science, **85,** 263–264, 1937.
[48] Thompson, M. H.: Arachnidism of Spider Poisoning. Kentucky Med. Jour., **33,** 340–341, 1935.
[49] Townsend, L. H.: The Black Widow Spider. Science, **84,** 392–393, 1936.
[50] Tripp, A. B.: Arachnida Bite of the Genital Area: A Case Report. Memphis Med. Jour., **13,** 106–107, 1938.
[51] Vaughan, J. T.: Arachnidism: Report of Two Cases. Virginia Med. Month., **57,** 806–807, 1931.
[52] Walsh, G., and Morgan, W. G.: Arachnidism. Amer. Jour. Med. Sci., **186,** 413–418, 1933.
[53] Walsh, G.: Arachnidism: A Case of Poisoning from the Bite of Latrodectus Mactans. South. Med. Jour., **23,** 1038, 1930.
[54] Walsh, G., and Hargis, A. S.: Arachnidism. South. Med. and Surg., **97,** 673–677, 1935.
[55] Wright, J. B.: Black Widow Spider Bite: Report of Four Cases. Jour. of Tennessee State Med. Assn., **28,** 6–7, 1935.
[56] Young, R. C.: Black Widow Spider Bite: Immediate Relief of Symptoms by Intravenous Administration of Gluco-Calcium. Tri-State Med. Jour., **9,** 1782, 1937.

SEBACEOUS GLAND CARCINOMA

ASA BEACH, M.D., AND A. O. SEVERANCE, M.D.

SAN ANTONIO, TEXAS

THIS PAPER is a discussion of an interesting malignant tumor of sebaceous gland origin, with a case report of such a tumor that arose in the fifth toe of the right foot. We feel that the location, the somewhat unusual type of tumor, and the problem arising in the choice of treatment are worthy of reporting.

Since the type of therapy for tumors depends upon their histology, the pathologic diagnosis should be accurately determined. Tumors that may metastasize demand some variations in treatment from those which do not. There are two divergent opinions regarding sebaceous gland tumors. Stout,[1] Darier,[2] and LaCassagne,[3] feel that these tumors resemble and behave like nonmetastasizing basal cell epitheliomata. Darier, and Favre, *et al.*[4] assume that the lipoid material in these tumors is a degenerative change in the tumor cells. Stout is in favor of the view that the sebaceous epithelioma is simply a specialized form of the basal cell group of tumors in which there is some tendency for the cells to reproduce sebaceous epithelium. On the other hand, Hagedoorn,[5] and Pages *et al.*[6] believe that they are malignant tumors of sebaceous gland origin and may metastasize.

About the middle of the last century, Malherbe and Robin[7] first recognized cancers coming from sebaceous glands; however, the first reported case of which we find a complete record was that of Allaire,[8] in 1891. In 1922, Menetrier and Ischwall[9] reported two similar tumors occurring on the ala of the nose and on the chin in a man, age 50. In a discussion of this paper, Darier said they were only basal cell epitheliomata. Masson and Gery,[10] in 1922, reported four sebaceous epitheliomata, one of the forehead, one of the ala of the nose, and two of the scalp. These authors are of the opinion that many basal cell tumors come from sebaceous glands and in most instances display regressive metaplasia and lose their sebaceous characteristics. When they retain these lipoid elements they are considered true sebaceous epitheliomata. Masson expresses the belief that any epidermal cell is totipotential and may give rise to a sebaceous epithelioma, so that it is not necessary to have sebaceous glands in a region from which a sebaceous epithelioma arises. In 1924, Grynfeltt[11] reported an ulcerated tumor of the ala of the nose. It was his opinion, however, that this tumor was a basal cell epithelioma containing areas of the sebaceous type. While it is generally accepted that the average basal cell tumor does not metastasize, nevertheless it must be borne in mind that such tumors can, but rarely do, metastasize. We are able to accept as proven examples the cases reported by Beadles[12] (one case), Finnerud[13] (two cases), and Mulzer[14] (two cases). Forty cases of sebaceous epithelioma of the eyelids were collected in 1926 by Morax;[15] no details were given. He added one case of his own. Hagedoorn,[5] in 1934, collected 59 cases of sebaceous epitheliomata of the eyelid, and also added another case to the literature.

Metastasis occurred in the cervical nodes in his patient four years after surgical treatment of the primary tumor. We assume that Morax's cases are included in Hagedoorn's collection. Prior to 1934, eight sebaceous gland carcinomata were reported, by five authors, in locations other than the eyelids. Since this contribution in 1934, 14 additional cases have been recorded by various authors.

Sourdille,[8] in 1894, was the first author to report metastasis. This occurred in the preauricular lymph nodes. He also was the first to report local recurrence which followed operation upon an upper eyelid tumor.

Allaire,[8] in 1891, was the first to use surgery on a sebaceous gland cancer. Without knowledge of the details of Morax's cases we credit Hughes[16] as the first to use radium therapy, which he tried in 1932, following five unsuccessful operations. Hagedoorn,[17] in 1937, used radium as initial therapy; this was followed in nine months by surgery for the recurrence. In 1938, Pages, *et al.*[6] first reported the use of roentgenotherapy. It was directed to the metastasis and postoperative local recurrence of the eyelid growth, with apparent success.

While not conducting an exhaustive review of the literature, we have, however, obtained the following information from available sources. Most of the patients were males over fifty years of age, with involvement of the eyelid, principally the upper lid. Other locations include ala of the nose, scalp, forehead, ear, chin, mammary region, scapular region, eyebrow, and scrotum. For the most part the tumors were of slow growth. The treatment in the majority of the cases was excision. Recurrence after treatment of the primary tumor was noted 34 times in 18 cases. In the literature there is mention of metastases having occurred five times in 40 cases.

Case Report.—A white male, age 60, was first examined October 5, 1939. He gave a history of a gradual enlargement of the right fifth toe that was first noticed two years previously. From time to time the toe suffered slight trauma. The first evidence of more rapid enlargement was noticed in May, 1939; this occurred after an injury, more severe than usual. While not painful the toe eventually became uncomfortable because of pressure from his shoe. There was no recent loss in weight. F.H.: There was no evidence of cancer, tuberculosis, or diabetes. P.H.: There was no history of acute or chronic disease since childhood.

Physical Examination.—The local examination showed a hard, smooth, partially encapsulated tumor of the fifth toe, right (Fig. 1), measuring 4x3x3 cm. Palpation failed to demonstrate definite connection with either phalanx. Firmly adherent skin on the plantar surface was faintly blue; elsewhere the color appeared normal. On the medial part of the plantar surface was a small superficial lesion that suggested a mild fungus infection.

Several freely movable, shotty inguinal lymph nodes were found in each groin. In the inferior portion of Scarpa's triangle, on the right side, was a hard, somewhat movable node, measuring 1.5x1 cm. Roentgenologic examination showed a soft tissue tumor of the right fifth toe. In the central portion there were foci of calcification; no bone involvement was seen (Fig. 2). *Clinical Diagnoses Considered.*—(1) Giant cell tumor of tendon sheath origin. (2) Fibrosarcoma. (3) Lymphangioma.

Treatment.—Dr. Asa Beach. The tumor of the toe was enucleated October 7, 1939; and after histopathologic study a subsequent operation was performed October 10, 1939.

This consisted of disarticulation at the metatarsophalangeal joint. Wound healing was normal.

Pathologic Examination.—Gross: Dr. A. O. Severance. The specimen (Fig. 3) is a tumor mass measuring 4x3.3x2.5 cm. It is covered on all but one surface by thick skin. The portion of tumor not covered by skin is a pinkish-gray, mottled with small yellow areas. A tendon attachment, one centimeter in length, enters the tumor in this region. The cut surface of the tumor has a creamy-gray appearance, with a diffuse distribution of small yellow areas. Deposits of calcium and zones of dense tissue are encountered although most of the tumor is soft.

Microscopic.—Eight sections taken from different parts of a slice through the center and from the region of incision are essentially similar. The tumor cells are arranged in fairly large, solid masses, small cords, clusters, and in a few instances in true acini (Fig. 4). The supporting stroma is dense fibrous connective tissue in which are seen areas of granular degeneration of the collagen, slight round cell infiltration, and foci of calcification. Tumor cells are seen in lymphatics and in one slide, prepared by Masson's trichrome method, a blood vessel is filled with tumor cells. Some parts of the tumor show central degeneration. In some of the larger masses a central grouping of large, pale cells is seen (Fig. 5). The tumor extends to the line of incision in one section, and actually invades a tendon. It does not invade the skin.

The individual tumor cells vary moderately in size and shape, have finely granular eosinophilic cytoplasm, and round to oval nuclei, with a slight to moderate amount of uniformly distributed chromatin and occasionally small nucleoli. Some of the cells are typical foam cells with light neutrophilic cytoplasm. In the sudan III preparation these cells contain many droplets of lipoid and stain bright orange. Many of the other eosinophilic granular tumor cells also contain lipoid as shown in this fat stain. Even cells in mitosis contain lipoid material in their cytoplasm. Mitotic figures are abundant, varying from none to five per high power field and averaging two. In a few of the masses there is a slight tendency to show palisading of cells perpendicular to the basement membrane. In the stroma there is a moderate infiltration of lymphocytes. Sections taken through the wound of the toe following amputation, do not show persistent tumor cells. *Pathologic Diagnosis:* Sebaceous gland carcinoma. (The essential pathologic features of this tumor have been studied and the diagnosis confirmed by Drs. A. P. Stout, of New York, and Shields Warren, of Boston.)

Postoperative Course.—In view of the pathologic diagnosis the patient was observed and examined every two weeks with particular attention to the right inguinal lymph nodes. For a period of four months there was no noticeable increase in size; however, on April 15, 1940, six months following amputation, for the first time, a definite measurable increase in size of the hard node, measuring 2.5x2 cm. was demonstrated.

A consultant concurred in the opinion that a radical inguinal adenectomy was advisable, and on April 27, 1940, a solid block dissection of the right groin was performed, from above downward. The only postoperative complication was prolonged drainage of lymph from the upper part of the wound.

Pathologic Examination.—Gross: The tissue from the right groin is a fairly large triangular-shaped mass of fat, measuring 13.5x11.5 cm. (Fig. 6). From this, 16 lymph nodes were isolated, varying from 3 to 20 Mm. in diameter. The largest node shows small satellite nodules of tumor extending out through its capsule.

Microscopic.—Seven of the 16 nodes contain tumor. In general, the metastases resemble the primary tumor. The tumor in the nodes is less differentiated, contains more mitotic figures per high power field on an average, and contains less lipoid material in fewer tumor cells as shown by the scharlach R stain. Some of these lipoid-containing tumor cells are in mitosis. Three of the nodes are completely replaced by tumor and dense fibrous stroma.

Postoperative Therapy.—The use of roentgenotherapy, for possible tumor extension

FIG. 1.

FIG. 2.

FIG. 1.—Photograph of tumor of fifth toe before operation.
FIG. 2.—Anteroposterior and lateral roentgenograms of toe tumor showing faint shadows of calcareous deposits.

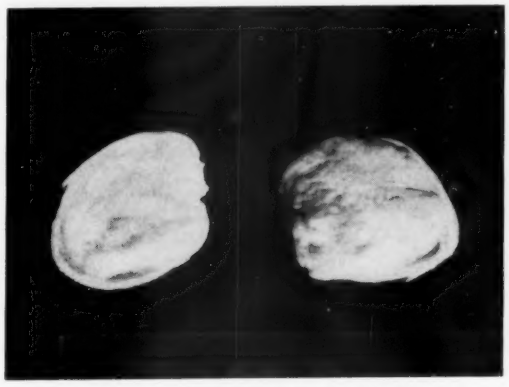


FIG. 3.—Photograph of tumor, in cross-section, after removal.

TABLE I

SUMMARY OF CASES APPEARING IN THE LITERATURE*

Author	Date	Sex	Age	Location	Duration	Treatment	Observation Notes and Results
Allaire[8]	1891	F.	11	Eyelid		Surgery	
Sourdille[8]	1894	M.	59	U. eyelid		Curettage	Recurrence 12 days after curettage. Rapid growth. Metastasis to preauricular lymph nodes
Gross[8]	1896	M.	63	U. eyelid	1 yr.	Surgery 2 times	Recurrence 3 mos. postoperative. Recurrence excised
Scalinci[8]	1908	F.	56	U. eyelid	1 yr.	Surgery	Good results
Snell[18]	"	F.	63	U. eyelid	10 yrs.	Excision (1905) Exenteration (1906)	Recurrence with metastasis even after exenteration
Grignolo[19]	1909			U. eyelid		Surgery	Invasion of orbit
Grignolo[19]	1909			L. eyelid		Surgery	
Menetrier and Durand[20]	1920	F.	54	Nasal ala	Few yrs.		
Cavara[21]	1920	M.	67	U. eyelid	Few mos.	Exenteration with lymph node excision	Metastasis to preauricular lymph nodes. Recurrence 6 mos. postoperative. Died of tumor
Menetrier and Ischwall[9]	1922	M.	50	Chin and ala			
Masson and Gery[10]	1922	M.	63	Forehead			
Masson and Gery[10]	1922	M.	50	Scalp		Surgery	Postoperative recurrence
Masson and Gery[10]	1922	M.	79	Nasal ala			
Masson and Gery[10]	1922	M.	72	Scalp			
Bazy[10]	1922	M.		Scrotum		Surgery	Postoperative recurrence
Riva[22]	1922	F.	63	U. eyelid	10 mos.	Surgery	No recurrence
Letulle[23]	1923	M.	75	L. eyelid	13 yrs.	Surgery 2 times	Recurrence 3 yrs. after first operation. No metastasis. No recurrence 1 yr. postoperative
Michail[24]	1924	M.	67	U. eyelid	1 yr.		No metastasis
Grynfeltt[11]	1924	M.	50	Nasal ala	20 yrs.	Surgery 2 times	Recurrence 10 yrs. after first operation (1914) was excised
Morax[15]	1926	M.	74	U. eyelid	14 yrs.		Forty cases mentioned in lit.
Morax[15]	1926						Invasion of orbit
Shoje[25]	1929	F.	69	L. eyelid	5 yrs.	Surgery	Two postoperative recurrences
Lazarescu and Ionescu[26]	1930	M.	67	U. eyelid	2 yrs.	Surgery 3 times	Two recurrences. Well 2 mos. after last operation
Chaillous and Kalt[27]	1931	M.	48	U. eyelid		Surgery 3 times	Three recurrences. Well 1 yr. after last operation
Nastri[28]	1931	F.	57	U. eyelid	5 yrs.	Surgery 4 times	Six recurrences. Alive with persistent tumor
Hughes[16]	1932	M.	54	U. eyelid	4 yrs.	Surgery 5 times Radium 2 times	
Hagedoorn[5]	1934	M.	66	U. eyelid	2 yrs.	Surgery	Metastasis present 4 yrs. after operation. Died of tumor
Lebensohn[29]	1935	F.	43	U. eyelid	1 yr.	Surgery 4 times Radium 2 times	Each operation followed by recurrence. No tumor evident 4 months after radiumtherapy
Hagedoorn[17]	1937	F.	50	U. eyelid	2 yrs.	Surgery	Recurrence 9 mos. postoperative
Hagedoorn[17]	1937	M.		U. eyelid	3 yrs.	Radium first, then surgery	Recurrence 9 mos. after radiumtherapy
Hagedoorn[17]	1937			Eyelid	3 yrs.	Surgery	
Dupont[30]	1938	F.	61	Mammary region	4 yrs.	Surgery	Satellite tumors present
Pages *et al.*[6]	1938	M.	33	L. eyelid	3 wks.	Surgery first, then x-ray therapy	Metastasis present at operation. Recurrence and metastasis disappeared with roentgenotherapy
Lucien and Crehange[31]	1939	M.	41	Ear (lobe)	2½ yrs.	Surgery	Tumor had invaded parotid region
Dollfus[32]	1939	M.	46	L. eyelid	12 yrs.	Surgery and radium-therapy	Lymphatic invasion misroscopically. No disease 6 mos. later
Warren and Warvi[33]	1940	M.	69	Nose	18 mos.	Surgery 5 times, then radium, then x-ray and radium	Five recurrences after surgery and 2 after irradiation
Warren and Warvi[33]	1940	M.	75	L. eyelid	8 mos.	Surgery 2 times	Recurrence after first operation, none after second (1935)
Warren and Warvi[33]	1940	F.	70	Scalp	3 wks.	Surgery (1937)	No recurrence
Warren and Warvi[33]	1940	F.		Scalp	6 mos.	Surgery (1937)	No recurrence
Warren and Warvi[33]	1940	M.	70	Eyebrow	Many yrs.	Surgery (1939)	Rapid growth for 6 mos. prior to operation. No recurrence
Warren and Warvi[33]	1940	M.	63	Scapula region (r)	Few yrs.	Surgery (1939)	No follow up

* The information on the last six cases was furnished by Dr. Shields Warren and Dr. Wesley N. Warvi. More detailed descriptions of these cases will be forthcoming in the paper on skin appendage tumors by these authors.

FIG. 4.—Photomicrograph of sebaceous gland carcinoma of toe showing relationship to epidermis and general formation of the tumor. (Low power)

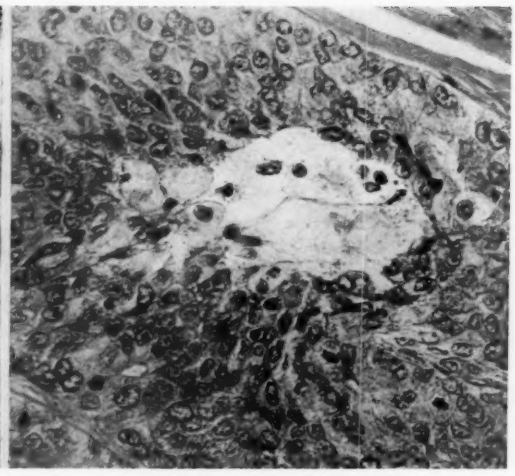


FIG. 5.—Photomicrograph of the tumor showing typical foam cells surrounded by the predominant type of tumor cells which contain several mitotic figures. (High power)

beyond the operative site, was considered. This treatment was strongly urged by Dr. A. P. Stout,[1] and it was instituted eight weeks after the groin dissection. The factors used were: 200 k.v., 25 ma., 50 cm., T-S-D, ½ mm. Cu. plus 1 mm. Al. filtration. Portals varied from 10x20 cm. to 15x20 cm. The pelvic and lumbar nodes were given 2,200 r. each, in daily doses of 200 r. Following a month's delay 2,200 r. were given to the operative site in 11 treatments.

Follow-Up.—Observation over a period of 13 months does not show any evidences of persistent disease, either locally, at each operative site, or in metastases. Subsequent follow-up 24 mo. after initial treatment shows no evidence of recurrence or metastasis.

FIG. 6.—Photograph of the deep surface of the block groin dissection showing the largest metastatic node cut in half.

COMMENT.—We feel that this tumor is of sebaceous gland type, and has behaved like any malignant glandular neoplasm. In view of the controversy which this statement is likely to arouse, it is well to review the prominent features of this tumor and others of its type. Scharlach R preparations show lipoid material in the typical foam cells, as well as in many of the other tumor cells, and even in those in active mitosis in the metastases as well as in the primary tumor. This latter is the first recorded notation, so far as we know, of this type of tumor cell containing lipoid while in mitosis. Definite

acinar formation is present. Tumor cells are seen in blood and lymphatic vessels—a finding rarely, if ever, noted in basal cell epitheliomata. The dense fibrous stroma, with calcification in this tumor is not unlike that seen in the scirrhous type of breast carcinoma. A characteristic common to basal cell tumors,

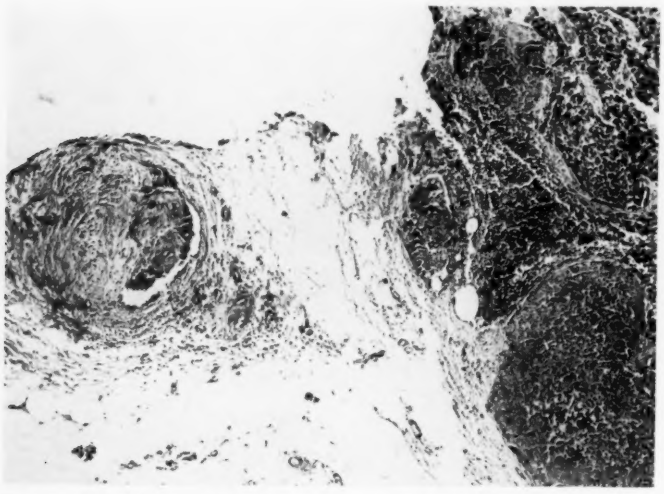


FIG. 7.—Photomicrograph showing tumor cells in an inguinal lymph node on the right, and within the lumen of a tangentially cut vein on the left.

namely, skin involvement, is strikingly absent in our case. The individual tumor cells do not resemble those seen in basal cell types for they have a more acidophilic cytoplasm, have a lighter staining nucleus, and show more variation in size and shape of the cells.

The difference in clinical behavior of the sebaceous gland carcinoma and basal cell epithelioma is shown by the increased incidence of metastases in the former. We knew of six instances of metastases in 75 cases of sebaceous gland carcinomata, whereas there are only five reported metastases of basal cell epitheliomata in the literature.

In this investigation, we have assumed that the glands of Zeiss and the meibomian glands are essentially similar to sebaceous glands. Certain ophthalmologists may raise the point that these eyelid glands are not true sebaceous glands. However, they are considered specialized derivatives of sebaceous glands, and tumors arising from both types are essentially similar in appearance and behavior.

An interesting feature of this tumor is its location in an area considered devoid of sebaceous glands. We have not encountered in the literature a tumor of this type in a similar location. Another feature worthy of mention is the history of recent rapid growth, the microscopic appearance of rapid cell proliferation, and the rapid development of metastasis.

We feel that in sebaceous gland carcinoma the treatment of choice is ade-

quate surgical excision of the primary tumor, with subsequent prophylactic regional node block dissection. In instances of clinical lymph node involvement a similar procedure should be carried out. In cases in which the nodes are involved, clinically or microscopically, proper roentgenotherapy should be administered to the area of the lymph node dissection as well as to nodes which drain this region.

The prognosis in our case is poor, in spite of the treatment given and the patient's apparent well-being at this time (eight and one-half months following groin dissection).

SUMMARY AND CONCLUSIONS

(1) Forty-one cases of sebaceous gland carcinomata, with our addition, have been reviewed. This excludes Morax's 40 cases.

(2) An unusual sebaceous gland carcinoma has been discussed.

(3) The proposed treatment is adequate surgical excision of the primary tumor; regional node dissection; and roentgenotherapy when indicated.

We are greatly indebted to Dr. Arthur Purdy Stout, of the Department of Surgery, College of Physicians and Surgeons, Columbia University, New York, N. Y., for his interest, advice, and cooperation in the treatment of this patient; and in the preparation of this communication.

We greatly appreciate the aid of Dr. John Pilter Heaney, of the Department of Surgery, Presbyterian Hospital, New York, N. Y., for his assistance in the review of the literature; and to Drs. Shields Warren and Wesley N. Warvi, of Boston, Mass., who have been very kind in allowing us the use of their six, as yet unpublished, cases of sebaceous gland carcinoma.

BIBLIOGRAPHY

[1] Stout, A. P.: Personal communications, December, 1939; May, 1940.

[2] Darier: Cited by Stout,[1] A. P.: Human Cancer, Lea & Febiger, Philadelphia, 1932. P. 549.

[3] LaCassagne, A.: Répartition des différentes variétés histologiques d'epithéliomas de la peau (plus particulièrement ceux de la tête) suivant les régions anatomiques, le sexe, et l'age. Ann. de dermat. et syph. vii sér., **4**, 407–514; 613–640; 722–754, 1933.

[4] Favre, M., Josserand, A., and Martin, J. F.: Nouvelle Pratique Dermatologique, vol. vi, Masson et Cie, Paris, 1936. P. 732.

[5] Hagedoorn, A.: Adenocarcinoma of a Meibomian Gland. Arch. Ophth., **12**, No. 6, pp. 850–867, December, 1934.

[6] Pages, R., Stora, E., and Duguet, J.: Epithélioma sébacé primitif des glandes de Meibomius. Bull. Soc. d'opht. de Paris, **50**, 621–623, December, 1938.

[7] Malherbe and Robin: Cited by Favre, *et al.*; in Nouvelle Pratique Dermatologique, vol. vi, Masson et Cie, Paris, 1936. P. 780–786.

[8] Allaire, Sourdille, Gross, Scalinci; Each cited by Lagrange, F.: Traité de la tumeurs de l'oeil, Paris, Steinheil, 1904, **2**, 733–739.

[9] Menetrier, P., and Ischwall, P.: Epithélioma sébacé. Bull. Assoc. franç. p. l'étude du cancer, **11**, 144, 1922.

[10] Masson, P., and Gery, L.: Epithélioma sébacé. Bull. Assoc. franç. p. l'étude du cancer, **11**, 284–295, 1922.

[11] Grynfeltt, E.: Un cas d'epithélioma baso-sébacé. Bull. Assoc. franç. p. l'étude du cancer, **13**, 474–489, 1924.

[12] Beadles, C. F.: Rodent Ulcer. Tr. Path. Soc., London, **45**, 176–181, 1894.

[13] Finnerud, C. W.: Metastatic Basal Cell Carcinoma of Skin (Two Cases). J.A.M.A., **82,** 775, 1924.

[14] Mulzer, P.: Two Cases of Typical Basal Cell Carcinoma and Consecutive Extensive Glandular Metastases. Klin. Wchnschr., **9,** 2086, 1930.

[15] Morax, V.: Cancer de l'Appareil Visuel. Doin et Cie, Paris, 1926. P. 101–112.

[16] Hughes, C. A.: Multiple Chalazia Showing Malignancy. Tr. Ophth. Soc. U. Kingdom, **52,** 557–558, 1932.

[17] Hagedoorn, A.: Adenocarcinoma of a Meibomian Gland. Arch. Ophth., **18,** No. 1, 50–56, July, 1937.

[18] Snell, S.: Carcinoma of Orbit Originating in a Meibomian Gland. Tr. Ophth. Soc. U. Kingdom, **28,** 144–147, 1907–1908.

[19] Gringnola: Di un caso epiteliomo primitivo delle ghiandole di Meibomio. Ophthalomologica, **1,** 250, 1909.

[20] Menetrier, P., and Durand, A.: Epithélioma sébacé. Bull. Assoc. franç. p. l'étude du cancer, **11,** 144–153, 1922.

[21] Cavara, V.: Epiteliomo primitivo delle ghiandole di Meibomio. Arch. per le sc. med., **43,** 1, 1920.

[22] Riva, G.: Epitelioma delle ghiandole di Meibomiane. Arch. di ottal., **29,** 261, 1922.

[23] Letulle et de la personne: Sebaceous Adenocancer of Meibomian Glands with Primary Sebaceous Carcinoma of Palpebral Conjunctiva. Arch. d'opht., **40,** 641, 1923.

[24] Michail: Epithélioma sébacé primitif des glandes des Zeiss. Ann. d'ocul., **161,** 817, 1924.

[25] Shoje, Y.: Un cas d'epithéliome primitif de la glande de Meibomius. Arch. d'opht., **46,** 144, 1929.

[26] Lazarescu, D., and E., and Ionescu, E.: A Case of Epithelioma of the Meibomian Glands. Brit. Jour. Ophth., **14,** 588–594, November, 1930.

[27] Chaillous, J., and Kalt, M.: Tumeur Meibomienne recidivante. Bull. Soc. d'opht. de Paris, **9,** 771–776, 1931.

[28] Nastri, F.: Epitelioma Meibomiano diffuso a tutto il tarso della palpebra superiore, operato con blefaroplastica alla Landolt Cirincione. Zentralbl. f. d. ges. Ophth., **28,** 647–648, 1931.

[29] Lebensohn, J. E.: Primary Carcinoma of the Meibomian Gland. Am. Jour. Ophthal., Series 3, **18,** No. 6, 552–554, 1935.

[30] Dupont, M. A.: Bull. Soc. franç. de dermat. et syph., **45,** 704–709, 1938.

[31] Lucien, M., and Crehange, J.: Sebaceous Epithelioma; with Report of a Growth in Lobe of Ear. Bull. Soc. franç. de dermat. et syph., **45,** 260–263, 1939.

[32] Dollfus, E. *et al.*: Epithélioma Meibomien d'aspect anormal. Bull. Soc. d'opht. de Paris, **51,** 23–26, 1939.

[33] Warren, S., and Warvi, W. N.: Personal communication, October, 1940.

NEUROPATHIC ARTHROPATHY OF THE ANKLE JOINT RESULTING FROM COMPLETE SEVERANCE OF THE SCIATIC NERVE

GRAHAM KERNWEIN, M.D. and W. F. LYON, M.D.

CHICAGO, ILL.

FROM THE DEPARTMENT OF SURGERY, NORTHWESTERN UNIVERSITY, ST. LUKES HOSPITAL, CHICAGO, ILL.

NEUROPATHIC JOINTS develop in approximately 10 per cent of all tabetic patients. The condition was first reported by Charcot[1] (1868), and described by him as joint destruction due to abnormal stimuli, transmitted through so-called trophic nerves. In 1888, Schultze and Kahler[2] reported similar lesions occurring in syringomyelia, and according to Schlesinger[3] the condition occurs in 30 to 40 per cent of all persons afflicted with that disease. Packard[4] reported the first instance of a neuropathic joint developing after a peripheral nerve injury. In his patient, arthropathies of the foot and knee followed compression of the sciatic nerve by a tumor. Although syringomyelia and tabes remain the two principal causes, neuropathic joints have been reported as developing in conjunction with a wide variety of clinical conditions. For a review and classification of these the reader is referred to a recent report by Shands.[5]

There are numerous reports of neuropathic joints purported to be the result of a peripheral nerve injury.[6, 7, 8, 9] Most of them are open to question, however, since the nature of the peripheral nerve injury is usually not clear and it is difficult to exclude the possibility of a central nervous system lesion. In fact Milgram[10] doubts the existence of a neuropathic joint as the result of a peripheral nerve injury.

The following case of neuropathic joint is reported because it throws light on the pathogenesis of that condition:

Case Report.—M. L., white, male, age 22, was struck in the left thigh by a red-hot rod, December 10, 1936. The resultant shock was treated in a local hospital. Three days later the patient was removed to St. Lukes Hospital and admitted to the service of Dr. W. F. Lyons.

Examination of the limb revealed that the red-hot iron had pierced the soft parts of the posterior portion of the left thigh at about the junction of the middle and lower thirds. It then had seared its way outward posteriorly, completely severing the sciatic nerve and all the hamstring muscles, but sparing the popliteal artery. The resultant soft tissue defect was approximately 15x10x4 cm. The ends of the sciatic nerve were separated by at least 6 cm. The patellar tendon reflex was active; the achilles tendon reflex absent. There was paralysis in the sensory and motor distribution of the sciatic nerve below this point.

Treatment with warm moist saline dressings was instituted and the wound responded promptly. Skin grafts were applied and by February 20, 1937, the wound was completely healed. The patient was discharged from the hospital, walking with the aid of crutches.

Knee joint stability was maintained by the intact quadriceps muscle group. The ankle joint was ataxic, anesthetic and relaxed.

Despite these handicaps, he soon learned to walk without aid. He returned to work in August, 1937. As a result of weight-bearing on, and undue traumatization of, this relaxed, paralyzed and anesthetic ankle joint, there soon developed a marked varus deformity, accompanied by a dependent edema.

Late in February, 1938, there appeared, quite suddenly, more than the usual amount of swelling. The patient remained in bed with the limb elevated. During the ensuing week he developed chills and fever. Three weeks later, April 11, 1938, having failed to improve, he was readmitted to St. Lukes Hospital.

Except for the left leg, the physical findings were negative.

On the posterior surface of the left thigh was a constricting cicatrix, 10 cm. wide. It began just above the popliteal space and extended proximally for a distance of 15 cm. The upper 4 to 5 cm. of this scar were hyperesthetic; the remainder hypesthetic. Below the lower border of the patella, the portion of the limb innervated by the sciatic nerve was completely paralyzed and anesthetic. The soft tissues here were markedly swollen. They did not pit but had the brawny resistance usually associated with lymphedema. The ankle region was huge and fluctuant. Some of the fluid was removed for culture and microscopic examination.

MEASUREMENTS

	Left	Right
Midtarsal joint region	24 cm.	20 cm.
Maximum ankle circumference	48.8 cm.	25.4 cm.
Circumference of calf	43.8 cm.	37.5 cm.

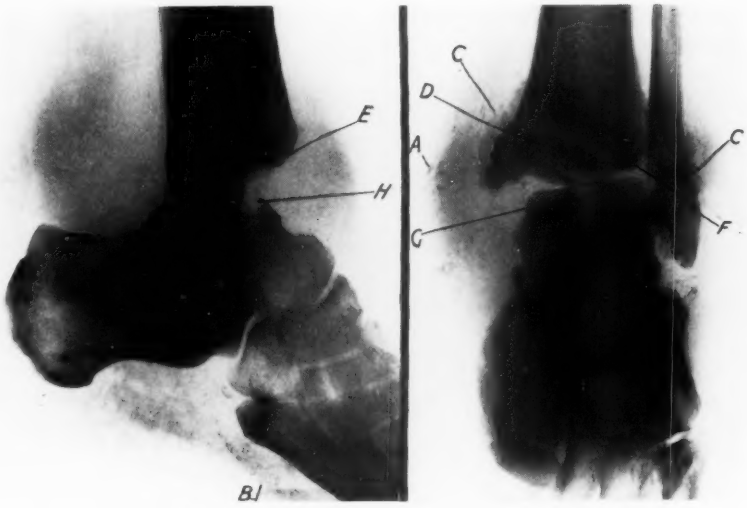
The foot lay at rest in an inverted position. Manipulation of the foot revealed complete absence of supportive structures of the ankle joint, with resultant markedly increased range of motion. In addition, a distinct crunching type of crepitation was felt.

Roentgenologic Examination.—Confirmatory, roentgenologic evidence of the relaxation of the ankle joint, noted on physical examination, is found in the altered configurations of the joint. There is moderate separation of tibial and astragalar shadows in the mesial and anterior portions of the angle joint. The foot is so plantar flexed that at the angle the AP view is taken, both the anterior and posterior lips of the articular surface of the tibia are visualized.

The size of the shadow cast by the soft tissues is increased, particularly in the lateral view. The increased density of the shadow about the ankle joint proper and obliteration of the shadow of the intermuscular fat planes, attests the presence of a joint effusion with rupture into the surrounding tissues. Disseminated throughout this effusion shadow are many discrete regions of greater density. (A) Their irregularity in size and shape is due to their origin. They were found to be particles of bone fractured from the joint surfaces and floating freely in the joint. In the lateral view, shadows of numerous discrete particles are clustered together along the plantar surface of the foot to form a well circumscribed band (B). This is the sheath of the flexor hallucis longus tendon, distended with fragments of bone and blood.

Radiating spicules of periosteal new bone are seen along the mesial cortex of the tibia and lateral cortex of the fibula (C). There is some hazy increase in density of the interior of the lower 2.5 cm. of the tibia. In the AP view of the lateral half of the tibial articulating surface, the bony articular cortex casts a dense, regular shadow. Mesially the shadow of the bony articular cortex is reduced in density. Here, there is a well-circumscribed region of moderately decreased density about 1.5 cm. in diameter which is not seen in the lateral views (D). The shadow cast by the tip of the internal maleolus is irregularly eroded and the size of the maleolus reduced.

Evidence of marginal erosion of the cortex is seen in the lateral view of the anterior surface of the tibia (E) and in the AP view of the lateral surface of the tibia (F) and in the mesial surface of the astragalus (G). In the AP view, the shadow of the bony



A B

FIG. 1.—AP. and lateral view of ankle: Disseminated throughout the soft tissue shadows are numerous discrete regions of greater density (A), the remnants of bony particles fractured from the joint surfaces. Similar particles filled the distended sheath of the flexor hallucis longus and their shadows form a discrete band (B) seen in the lateral view. Radiating spicules of periosteal new bone (C) are seen on mesial surface of tibia and lateral surface of fibula. A well-circumscribed region of decreased density (D) is seen on the mesial articular surface of the tibia; laterally, the bony articular cortex casts a dense, regular shadow. Marginal erosion is seen at E, F, G. The shadow of the bony articular cortex of the astragalus as seen in the lateral view is partially destroyed anteriorly. In the underlying bone there is an irregularly-shaped region of decreased density about 1 cm. in diameter (H).

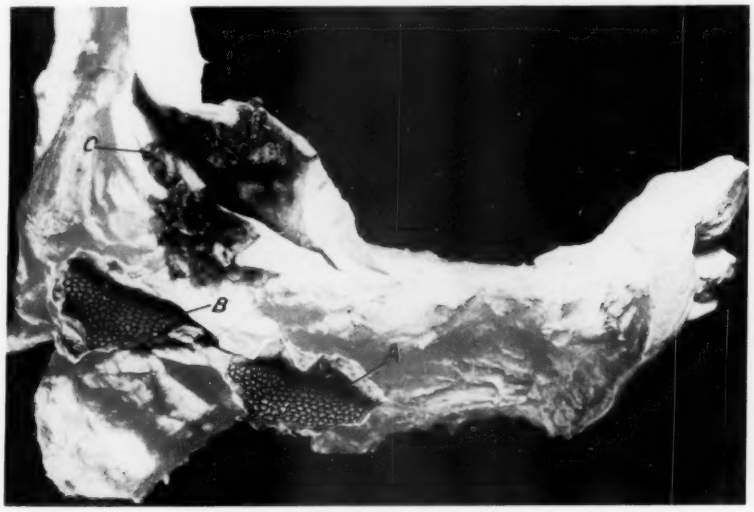


FIG. 2.—Photograph of the gross specimen with most of the soft tissues dissected away. The tendon sheath of the flexor hallucis longus (A) has been blocked out, and the nodules (B) studding its lining have been retouched. (C) An oval defect in the anterior mesial surface of the tibial cortex. Externally, it communicated with the extensor tendons of the toes. Internally, it communicated with a cavity in the tibia which is seen as region of decreased density (D) in Figure 1.

articular cortex is hazy over most of the articulating surface of the astragalus. The shadow of the bony articular cortex of the astragalus, as seen in the lateral view, is partially destroyed, anteriorly. In the underlying bone there is an irregularly-shaped region of decreased density about 1 cm. in diameter (H). The smaller tarsal bones and joints are essentially unchanged. *Roentgenologic Diagnosis:* Neuropathic joint.

Laboratory Data: R.B.C. 3,490,000; Hb. 12.4 Gm.; W.B.C. 10,000. Blood culture, neg.; Wassermann and Kahn tests, neg.; fluid aspirated from ankles; cultures, smears and stains for T.B.C. and pyogenic organisms, neg. Sedimentation rate: 15 mins. 7 Mm.; 30 mins. 24 Mm.; 45 mins. 26 Mm.; 60 mins. 27 Mm.

Because of the complex clinical picture, that is, elephantiasis as a result of the constricting thigh cicatrix, loss of sensory and motor nerve supply throughout the sciatic distribution below the patella, and marked bone and joint changes, the leg was amputated at the knee May 4, 1938.

Pathologic Examination.—Gross: The specimen consisted of a lower limb, disarticulated through the knee joint, devoid of skin and subcutaneous tissues in the proximal 15 cm. (stump flaps). The skin had the distinct *"peau d'orange"* appearance, and the soft parts the brawny resistance characteristic of lymphedema. There was no pitting edema. The diameter of the leg was increased throughout, being greatest in the ankle region where it measured 42 cm. in circumference. The foot was in a moderately inverted position, dorsi and plantar flexion were increased, and there was a marked crunching crepitation associated with the abnormal, lateral motion which was present.

Beginning 3 cm. above the internal maleolus, the sheath of the flexor hallucis longus was enlarged (Fig. 2). It extended below the maleolus and forward along the plantar surface of the foot, to end 2.5 cm. from the point of insertion of the tendon. It was filled with fragments of detached bone and clotted blood (Fig. 1B). Connecting this sheath with the distended joint capsule, mesially, there was a sinus 0.5 cm. in diameter. Another sinus extended out into the subcutaneous tissue, posteriorly, to end blindly. The wall of the sheath was 1.2 cm. thick, and the lining was studded with myriads of nodules from 0.1 to 0.3 cm. in diameter and elevated 0.1 to 0.2 cm.

Microscopically, the tendon sheath was composed of two quite distinct layers. The outer, 0.6 cm. thick, was loosely arranged, edematous fibrous tissue. Disseminated throughout were numerous blood vessels. Lining each of these vessels was a single layer of cuboidal endothelial cells. Clustered about these capillaries were foci of chronic inflammatory cells, small round cells and plasma cells predominating. Some macrophages, containing large, brown-staining granules were also seen.

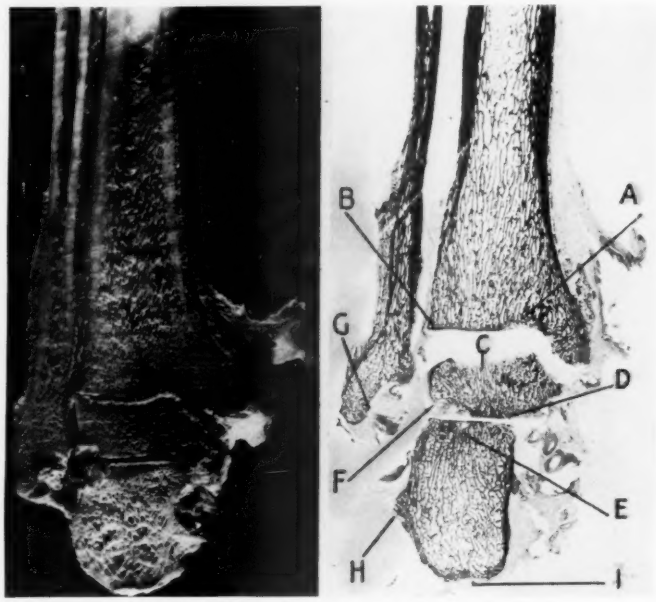
The inner layer was also approximately 0.6 cm. thick The surface was thrown into folds comprising the nodules, seen grossly (Fig. 2B). They consisted of myriads of closely packed erythrocytes, polymorphonuclear neutrophils, round cells and plasma cells lying in a loosely arranged fibrillar stroma. In addition, disseminated throughout, were spicules of dead bone, their surfaces irregularly serrated. Near these spicules and in some instances lying in contact with them, were multinuclear giant cells of the foreign body type.

In the fatty and fibrous tissue below and behind this distended tendon sheath was an encapsulated hematoma about 3 cm. in diameter. The sheath of the peroneus longus tendon was enlarged to as much as 1 cm. in diameter throughout the 4 cm. just opposite the distal end of the fibula. It was filled with fragments of detached bone and clotted blood and connected with the joint by a sinus 0.3 cm. in diameter.

The capsules of the tibio-astragalar, subastragalar and fibula-astragalar joints were destroyed. Instead, one joint had been formed enclosed in a capsule which extended from the tibia to the calcaneous mesially, and from the fibula to the calcaneous laterally. It was filled with a viscid serosanguineous fluid, in which floated the astragalus and innumerable spicules of detached bone. The walls were 0.7 cm. thick and covered with clotted blood.

The ankle joint was exposed by cutting in a coronal plane through both malleoli at about their midportions. In this manner the calcaneous, the astragalus, the distal 13 cm. of the tibia and fibula as well as their respective joint surfaces were visualized (Fig. 3A). For purposes of description, the bones and their joints were divided into the nine regions as indicated in Figure 3B (a microscopic slide of the entire region).

In this plane the foot was in a moderate, varus position. The mesial side of the tibia was, therefore, the weight-bearing portion. Here the hyalin articular cartilage was completely destroyed for 3 cm., the underlying bone had been gouged out to form a



A B

FIG. 3.—(A) A coronal section through the lower third of the leg and underlying tarsal bones. The plane passes through the posterior margin of the cavity seen at D in Figure 1. (B) A microscopic section through the same coronal plane. Photomicrographs were made of the designated regions.

pyramidal-shaped defect, its base 3 cm. and its vertical height 2.5 cm. (Fig. 1D). The apex of this cavity opened through an oval defect in the cortex of the anterior mesial surface of the tibia and communicated with the sheaths of the extensor tendons of the toes (Fig. 2C). Filling this cavity and the distended tendon sheaths was a mass of blood and detached fragments of bone.

The microscopic changes in the joint surface at region A of Figure 3B are shown in Figure 4. There was a marked destruction of bone and cartilage without attempt at bony repair.

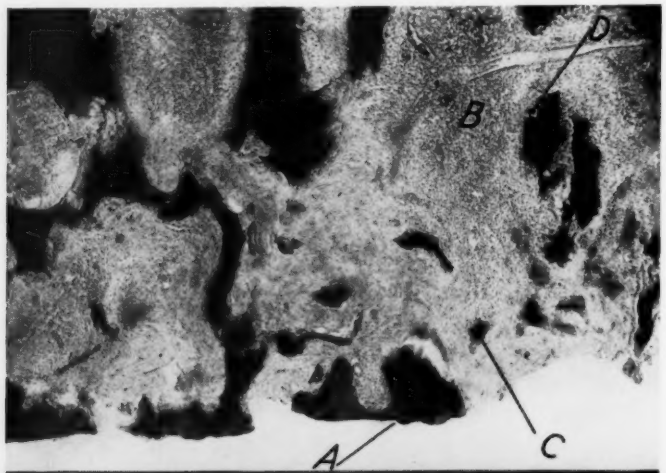
Laterally, in the nonweight-bearing portion, the hyalin articular cartilage, although preserved, was deeply pitted and thinned out to 1 Mm. or less (region B, Fig. 3B). Figure 5 is a photomicrograph of region B showing the junction of the mesial tibial cortex with the hyalin articular cartilage. The bone and cartilage were undergoing resorption by subchondral granulations. There was, however, a minimal amount of new bone formation.

The superior articulating surface of the astragalus was completely devoid of hyalin articular cartilage. The denuded spongy bone was stained red-brown with formalin-fixed blood and so shaped that the irregularities of its surface interdigitated with those of the tibia (region C, Fig. 3B and A). The marked destruction of bone and cartilage of the

superior articulating surface of the astragalus is seen in Figure 6. As the astragalus was floating in the pathologic joint space, it was without a blood supply. Despite this fact, only the bone sand was without lacunar cells. Considerable new bone formation was present in the deeper portions. Calcification of these osteoid deposits would help produce the characteristic sclerosis seen in the roentgenograms.

The subastragalar joint showed relatively few changes. The articular cartilage was deeply pitted and reduced to 0.1 to 0.2 cm. in thickness (region D, Fig. 3B).

FIG. 4.



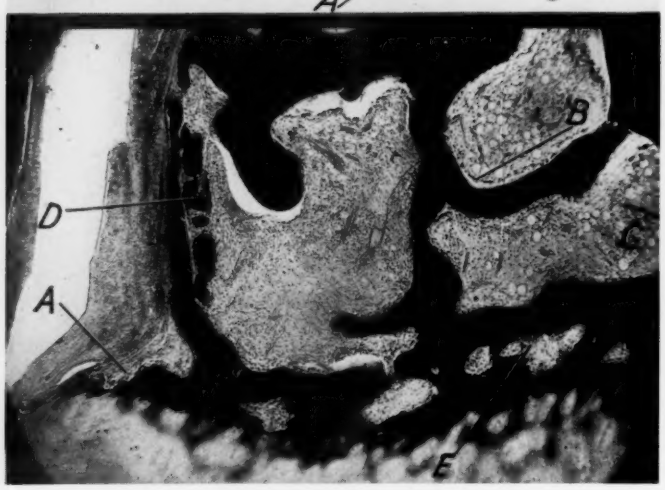


FIG. 5.

FIG. 4.—(Region A of Fig. 3 B): The bony articular cortex has been largely destroyed and only fragments of the calcified articular cartilage (A) remain. The marrow is densely fibrous and contains focal regions of round cell infiltration (B) as well as numerous spicules of bone sand (C). The surface of many of these latter is serrated with lacunae, in some of which giant cell osteoclasts are seen (D).

FIG. 5.—(Region B of Fig. 3 B): Marginally, there is subperiosteal and subchondral invasion by a chronic type of granulation tissue (A), with destruction of the articular cortex and beginning invasion of the articular cartilage. Osteoblasts are seen on the surface of some of the trabeculae (B). The marrow is a mixed fatty and fibrous type (C). Focal regions of degeneration of the marrow do not show in these photomicrographs. Immediately beneath the cortex there are a few spicules of newly formed endosteal bone.

Figure 7 shows the region of transition from living to necrotic cartilage, on the inferior articulating surface of the astragalus. Where the bony articular cortex was intact, the overlying cartilage cells and matrix stained well (A). The bony trabeculae beneath this region were hypertrophied (B). These trabeculae cast a denser than normal shadow in the roentgenograms. Thus, they too would contribute to the sclerosed appearance of some of the bone. Immediately adjoining this was the lateral limit of the area of this surface of the astragalus, which received the maximum trauma. Here the

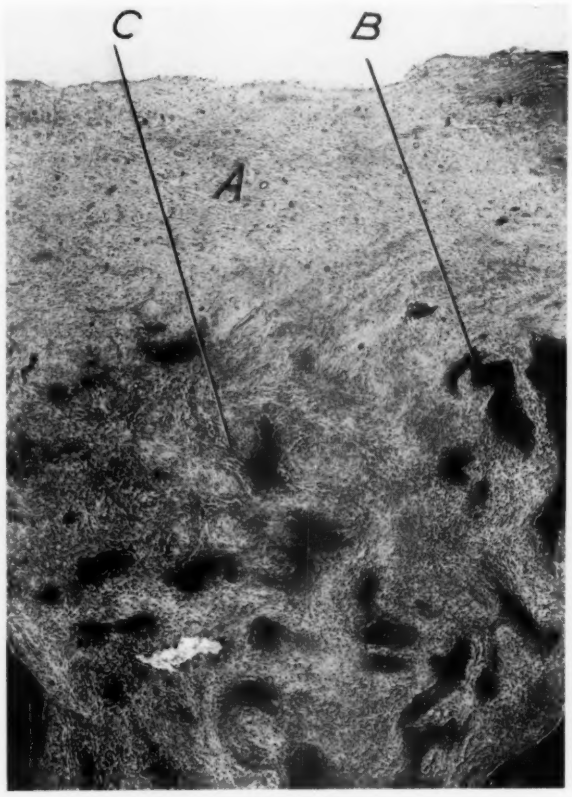


FIG. 6.—(Region C of Fig. 3 B): The articular cartilage and bony articular cortex have been completely destroyed. Instead, a densely fibrous type of tissue (A) covers the surface of the joint and fills the marrow spaces. In the depths are numerous fragments of so-called bone sand (B) and considerable osteoid tissue (C). In most instances the particles of bone sand act as a nucleus for the osteoblasts' activity.

cartilage was necrotic, its cells and matrix staining very poorly. This necrosis was the result of interference of nutrition from the synovia, but mostly from trauma. Subchondral granulations were present throughout the entire extent of this necrotic cartilage. They had destroyed most of the bony articular cortex and invaded and thinned the cartilage by absorption from below. Their presence here, as in rheumatoid and tuberculous arthritis, is best explained as a foreign body reaction to sequestrate and attack the necrotic cartilage.

Figure 8—region E, is a microscopic study of the opposing surface of the calcaneous. Regional hypertrophy of bony trabeculae, subchondral cavitation and marked destruction of the articular cartilage closely parallel the changes seen in degenerative arthritis.

A panus covered most of the articulating surface of the fibula and the marginal portion of the opposing surface of the astragalus. In the region of the panus, the cartilage had a fibrous appearance. The subchondral spongy bone of the tibia and fibula was stained red-brown with hemorrhage for a depth of as much as 1.5 cm. A similar discoloration was present throughout most of the astragalus and calcaneous. There was

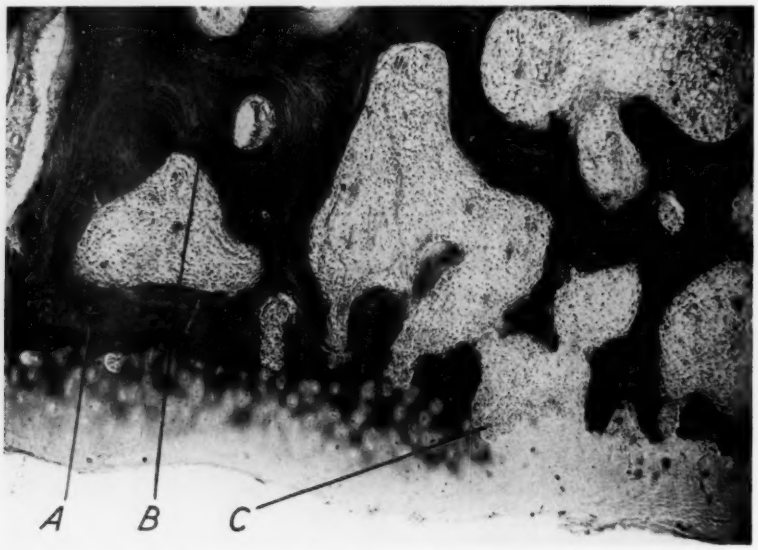


FIG. 7.—(Region D of Fig. 3 B): The articular cartilage is markedly thinned and its surface irregular and fibrous. In some places the bony articular cortex remains intact (A) and the underlying bony trabeculae are hypertrophied (B). In neighboring places (C) there is a densely fibrous type of granulation tissue which has destroyed the articular cortex and is invading and resorbing the overlying cartilage. Focal regions of degeneration and round cell infiltration are present but not seen at this power. Where the articular cortex is intact the articular cartilage stains well; where it is absent the articular cartilage stains poorly.

a subperiosteal bony thickening, some of which was ossified. This extended along the distal 9 cm. of the lateral surface of the fibula and distal 8 cm. of the mesial side of the tibia (X of Fig. 3A and B).

Figure 9 (region F of Fig. 3B) shows the inferior marginal portion of the lateral articular surface of the astragalus. Destructive changes were minimal, as this region was subjected to relatively little trauma.

Figure 10 (region G of Fig. 3B) shows the articular surface of the fibula. Despite the fact that this region was subjected to relatively little trauma, the changes in the cartilage were marked. A panus, containing numerous foci of round cells, covered the surface of the articular cartilage and was invading and destroying it. Subchondral invasion by granulations was minimal. These changes closely resemble those seen in proliferative arthritis.

Figure 3B—region H, shows a spur of periosteal new bone on both sides of the calcaneous. It was situated at the point of attachment of the joint capsule. These spurs were the result of elevation of the periosteum by the over distended and relaxed joint capsule. Figure 11 is a high power magnification, showing the lateral, periosteal spur and the underlying foci of endosteal new bone.

As a result of the peculiar gait of the patient, the base of the calcaneous was repeatedly traumatized. Evidence of this trauma is seen in the formation of periosteal new bone (region I, Fig. 3B and Fig. 12). This new bone may be likened to a very early calcaneal spur.

Lining the joint capsule is a markedly cellular and vascular granulation tissue. Disseminated throughout are numerous particles of bone sand, their lamellae devoid of cells and their edges deeply serrated by the osteoclastic activity of the surrounding granulation tissue. Present, also, are numerous large- and medium-sized foci of round cells giving it much the same appearance as has the synovial lining in rheumatoid arthritis.

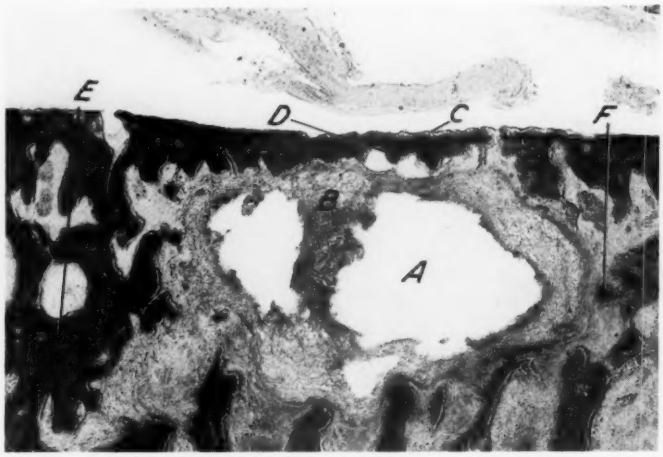


FIG. 8.—(Region E of Fig. 3 B): (A) is the subcortical cavity seen in Figure 3 B. It contains an inflammatory type of exudate (B). The overlying cartilage (C) and bony articular cortex (D) are largely destroyed. Laterally, the bony trabeculae are hypertrophied (E); mesially, the margins of the trabeculae are serrated, the marrow is fibrous and there is bone resorption (F).

Discussion.—There are three theories of pathogenesis advanced to cover some or all cases of neuropathic joints. The first, the chief proponents of which are Herndon,[11] McCallum[12] and Stargardt,[13] contend that neuropathic joints in tabetics develop as a result of injury to a nerve and a low grade spirochetal infection of the joint itself. Opposing this theory are the following facts: Careful search, in a large number of cases, has failed to reveal either the spirocheta pallida or other evidence of syphilitic infection; there is both clinical and experimental evidence that certain other factors, common to tabes and to syringomyelia, are really responsible for the development of neuropathic joints; the joint lesions seen in conjunction with syringomyelia and peripheral nerve injuries are similar in all respects to those present in Charcot's joints.

The second, the trophic theory, considers some disturbance in the nervous trophic regulatory mechanism as the factor of prime etiologic importance. In support of this theory, Warttenberg[14] cites the following pathologic alterations as being present in the neighborhood of unilateral Charcot's joints: Elevation of local temperature; rise in venous pressure; increase in oscillometric index; anomalies of sweat secretion; and disturbances in the pilometer reflexes.

That the central nervous system exercises a profound influence on the nutrition of all tissues seems certain. There is, however, no evidence of special

nerves whose function is merely trophic. The complex influence exerted by the central nervous system is seen in the limbs of individuals with a residual postpoliomyelitis paralysis. The skin becomes tense, thin, shiny, cyanotic and cold. The striated muscles atrophy and the supporting structures about the involved joints relax. In children, the bones not only become less dense, as demonstrated roentgenologically, but also decrease in circumference, a process known as concentric atrophy. Yet, despite these marked "trophic" changes, neuropathic joints do not develop. Sensation, the loss of which is common to all neuropathic joints, remains intact in poliomyelitis. As the individual is not ataxic, joint injuries are uncommon. In addition, once an injury occurs, the attendant pain causes the individual to protect the part and thus allow it to heal.

FIG. 9.—(Region F of Fig. 3 B): Articular cortex (A) preserved; overlying hyaline articular cartilage (B) stains well, is of about the usual thickness and has smooth surface. Underlying marrow (C) is of fatty type. Marginally, (D) there is subchondral invasion of articular cartilage and marked destruction of articular cortex. Here, the overlying articular cartilage (E) is thinned, stains poorly and its surface is slightly roughened.

The third, the mechanical theory, contents that neuropathic joints are the result of trauma to a joint, deprived of its sensation.

The results of severe trauma are so well-recognized, they need no comment. That prolonged trauma of a milder nature frequently produces bony changes is not as well-recognized. Brailsford[15] and Küntscher[16] have published roentgenograms showing the effect upon bones of prolonged rhythmic trauma produced by pneumatic tools. In Brailsford's patients, well-circumscribed regions of decreased density developed in the metacarpals and carpals. Küntscher[16] believed the bony disintegration he found in the weight-bearing portions of the condyles and head of the femur closely paralleled osteochondritis. As the nerve supply remained intact, these cannot be considered neurotrophic lesions.

Many individuals with classical tabes dorsalis, including ataxia, hypotonia and loss of deep joint sensibility, never develop neuropathic joints. Others, with bilateral sensory changes develop only unilateral neuropathies. In the latter, a history of trauma to the afflicted limb can usually be elicited. The severity of the injury is overlooked because of the absence of pain. Inadequate treatment results in the rapid development of a neuropathic joint. That

loss of joint sensation alone does not result in the development of neuropathic joints in the human is, therefore, apparent. That destruction of joint sensation by cutting the posterior roots does not suffice to produce a neuropathic joint in dogs, cats, or rabbits has been repeatedly confirmed.[17, 18, 19]

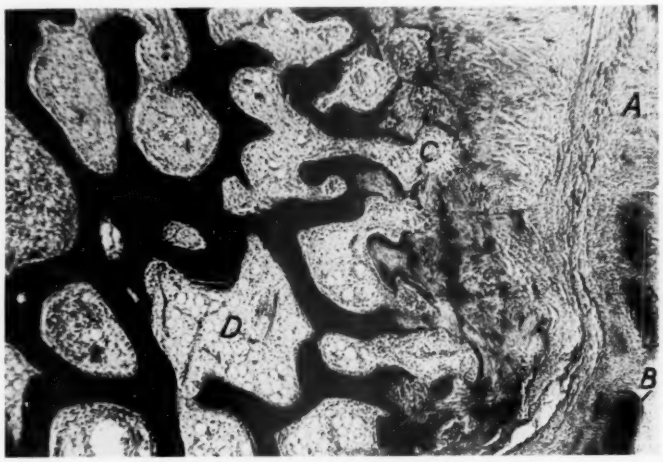


FIG. 10.—(Region G of Fig. 3 B): The surface of the articular cartilage is covered by a panus (A) which is invading and destroying the cartilage. Disseminated throughout this panus are foci of round cells (B). Regionally, the bony articular cortex has been destroyed by an immature type of subchondral granulation tissue (C) which, in addition, is invading and destroying the articular cartilage from below. The marrow (D) is of a mixed fatty and fibrous type. A layer of osteoblasts covers the surface of many of the trabeculae.

The case under consideration supports the mechanical theory. Severance of the sciatic nerve resulted in the development of a combined motor and sensory lesion. Changes appeared in the form of marked atrophy of the leg muscles and relaxation of the ankle joint due to loss of motor nerve supply. The sensory loss was characterized by a marked ataxia and anesthesia below the knee. The trauma, associated with the act of walking upon such a limb, was often excessive because of the absence of the protective sense of pain. This was sufficient to cause the joint to disintegrate.

Roentgenograms of the ankle joint revealed changes typical of those ascribed to neuropathic joints. There was marked destruction of the opposing joint surfaces with some sclerosis but no atrophy. Disseminated throughout the markedly enlarged joint were numerous fragments of bone. An unusual feature was the extra articular migration of the bone sand causing the shadows in the roentgenograms. As a result of stripping of the periosteum, by the distended capsule, radiating spicules of new bone were present on the lateral surface of the fibula and mesial surface of the tibia.

SUMMARY

A case is reported of severance of the sciatic nerve at midthigh, paralyzing the muscles of the leg and causing a loss of sensation to foot and back

of leg. Following active use of the limb, a neuropathic arthropathy developed in the ankle joint. The leg was amputated, and the diagnosis confirmed by pathologic examination. The case substantiates the theory that the changes are the result of excessive trauma to a relaxed anesthetic joint and favors the same theory of pathogenesis of these joints in tabes and syringomyelia.

FIG. 11.—(Region H of Fig. 3 B): The results of trauma attendant on the stretching and tearing of the capsule and ligaments are seen in the ossification of the external lateral ligament at its point of attachment to the calcaneus. Here, there is a spur of periosteal new bone (A) as well as several foci of endosteal new bone (B). At the level above the endosteal reaction, the marrow is fibrous (C) whereas below, the marrow is the usual fatty type.

REFERENCES

[1] Charcot, J. M.: Sur quelques arthropathies qui paraissant d'énpendre d'une lésion du cerveau on de la moelle épinière. Arch. de physiol. nor. et path., **1**, 161, 1868.

[2] Schultze, F., and Kahler, O.: Quoted by Shands.[5] Arch. Surg., **20**, 615, 1930.

[3] Schlesinger, H.: Die Syringomyelia. 2nd ed., Leipzig, 1902, pp. 93–140.

[4] Packard: Quoted by Mitchell, S. W. Trans. Path. Soc., Phila., October, 1863.

[5] Shands, A. R., Jr.: Neuropathies of the Bones and Joints: Report of Case of Arthropathy of Ankle Due to Peripheral Nerve Lesion. Arch. Surg., **20**, 615, 1930.

[6] Duncan, J. H.: Neuropathic Arthritis. J.A.M.A., **79**, 1987, 1922.

[7] Philips, H. B., and Rosenbeck, C.: Neuropathies: A Consideration of the Etiology and the General Characteristics with Special Reference to that Form Caused by Peripheral Nerve Disease or Injury. J.A.M.A., **82**, 27, 1924.

[8] Rosenbeck, C., and Philips, H. B.: Neuro-Arthropathies of Peripheral Nerve Injury Origin. J.A.M.A., **86**, 169, 1926.

[9] Oehlecker, F.: Zur kasuistik und zur behandlung neuropathisher gelenkerkrankungen. Beitr. z. klin. Chir., **65**, 63, 1919.

[10] Milgram, J. E.: The Arthropathies. Nelson's New Loose-Leaf Surgery, **3**, 182 E–182 N, 1927.

[11] Herndon, R. F.: Three Cases of Tabetic Charcot's Spine. Jour. Bone and Joint Surg., **9**, 605, 1927.

[12] McCallum, W. O.: Textbook of Pathology, 4th ed., Philadelphia. W. B. Saunders Company, 1928, p. 739.

[13] Stargardt, K.: Über die aetiologie der abischen arthropathien. Arch. f. Psychiat., **49**, 936, 1912.

[14] Wartenberg, R.: Neuropathic Joint Disease. J.A.M.A., **111**, 2044, 1938.

[15] Brailsford, J. F.: Pathological Changes in Bones and Joints Induced by Injury. Brit. Med. Jour., **2**, 657, 1936.

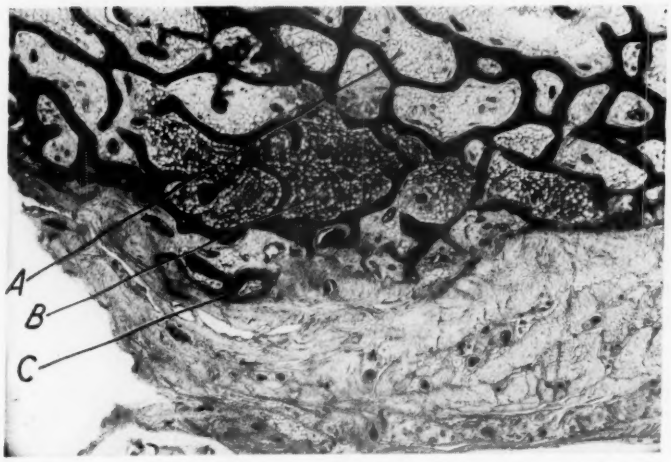


FIG. 12.—(Region I of Fig. 3 B): The cancellous spaces are filled with a fatty marrow (A) with the exception of the narrow strip of hematopoietic marrow (B). Some periosteal new bone formation is seen at C, the region which received the maximum traumatization. This latter may be likened to a beginning calcaneal spur.

[16] Küntscher, G.: Über das wesen der mechanisch bedingten knochen und gelenkerankungen. Arca. f. klin. Chir., **193,** 665–668, 1938.

[17] Eloesser, L. H.: Neuropathic Affections of Joints. ANNALS OF SURGERY, **66,** 201, 1917.

[18] Katsuki, S.: Beitrag zur experimentellen neuropathischen arthropathie und zugleich zu deren pathogenese. Ztschr. f. klin. Med., **130,** 567, 1936.

[19] Nozoe, M.: Experimentelle unter suchungen über die entstehung der arthropathia neuropathica. Arch. f. klin. Chir., **192,** 29, 1938.

PRIMARY RETICULUM CELL SARCOMA OF BONE

REPORT OF TWO CASES WITH BONE REGENERATION FOLLOWING ROENTGENOTHERAPY

CHAN SZUTU, M.D.,

AND

CHIH-KUANG HSIEH, M.D.

PEKING, CHINA

FROM THE DEPARTMENTS OF SURGERY AND RADIOLOGY, PEIPING UNION MEDICAL COLLEGE, PEKING, CHINA.

UNTIL RECENTLY reticulum cell sarcoma of bone has been considered a secondary lesion. That this neoplasm may be primary in bone was first demonstrated by Oberling[5] in 1928. Adequate corroboration of this thesis did not appear, however, until the recent publication of Parker and Jackson.[6] These authors reported 17 cases of bone tumor, including 13 cases from the Registry of Bone Sarcoma of the American College of Surgeons, in which they made the diagnosis of primary reticulum cell sarcoma. Most of these cases had been classified previously as osteogenic sarcoma, Ewing's sarcoma, Hodgkin's disease, lymphosarcoma, or inflammation. After careful review, Parker and Jackson believed each of these lesions identical histologically with reticulum cell sarcoma as seen in soft tissue, but pointed out certain characteristic differences in the clinical course. Simmons,[7] in a recent article, and Kuhns, *et al.*,[4] in the Sixty-ninth Report of Progress in Orthopedic Surgery, also discussed this group of tumors as primary lesions of bone. According to Ewing,[3] some of the 17 cases of pure reticulum cell sarcoma of bone reported by Craver and Copeland[2] were primary in this tissue. The Committee of the Registry of Bone Sarcoma also has recognized reticulum cell sarcoma arising in bone marrow as a distinct entity, and has recommended inclusion of this term in the newly proposed classification[3] of tumors of bone.

In the Peiping Union Medical College Hospital we have observed two cases which belong to this group of primary bone tumors, and consider them of sufficient interest to warrant reporting.

CASE REPORTS

Case 1.—A Chinese girl, age 21, was first seen April 30, 1932, in the Tumor Clinic of the P.U.M.C. Hospital, and complained of a swelling of the left shoulder region, which had been present for more than two months. From the beginning of 1930 she had experienced occasional pain shooting from the fingers to the shoulder on the left side. The pain occurred from one to four times a month, and lasted from a few minutes to a few hours on each occasion. In February, 1932, the patient noticed a steadily increasing swelling in the left shoulder region accompanied by constant pain, and a mass in the left arm pit. The motion of the left shoulder became gradually impaired until the loss of function was complete. Numbness in the left upper extremity was never present.

There was no history of sore throat, bleeding from the nose, headache, chronic

PLATE I.

Fig. 1

Fig. 2

Fig. 3

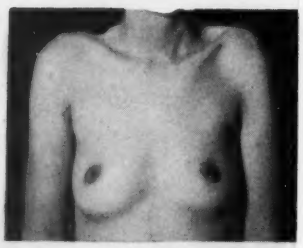


Fig. 4

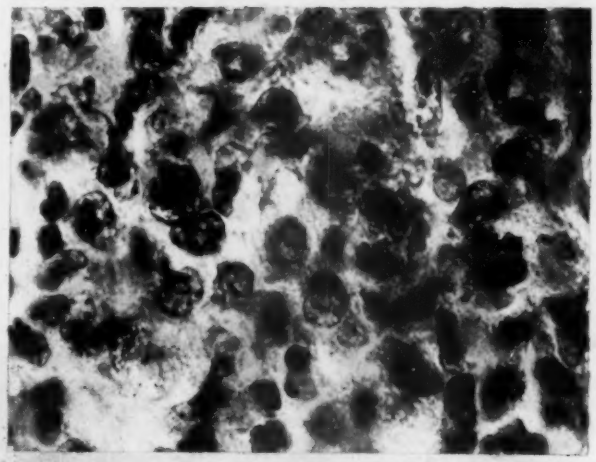


Fig. 5

FIGS. 1 and 2.—Case 1: Appearance of the tumor before treatment. Note the diffuse swelling of the shoulder and the neck and the mass in the axilla. The arm was slightly abducted.

FIGS. 3 and 4.—Case 1: Appearance of the tumor-bearing regions, six years and three and a half months after treatment. Note the small nodule of fibrous tissue in the axilla that has been stationary in size for several years. The atrophy of the shoulder muscles is evident.

FIG. 5.—Case 1: Photomicrograph of a cervical lymph node showing reticulum cell sarcoma before treatment. The tumor cells and their nuclei vary in shape, size and staining. The characteristics of a normal lymph node are absent. Hematoxylin-eosin stain. (×1,400)

cough, hemoptysis, or tumor elsewhere in the body. The general health apparently was not affected by the present illness. There was no history of cancer in the family.

Physical Examination.—The patient was well-developed and well-nourished; she

PLATE II.

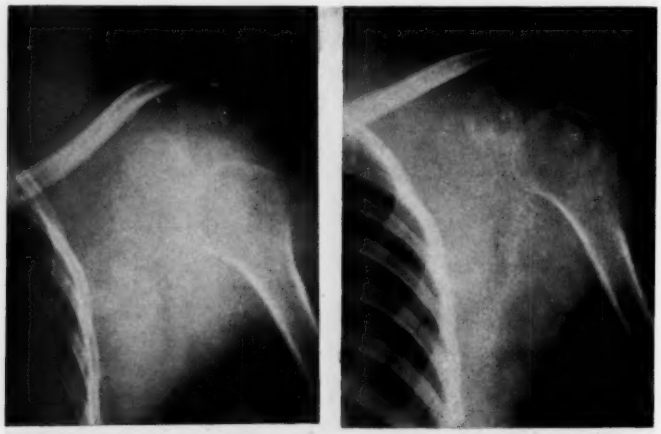


Fig. 6 Fig. 7

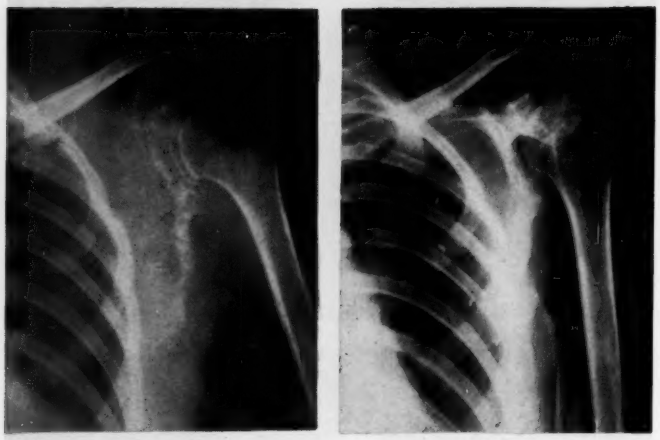


Fig. 8 Fig. 9

FIG. 6.—Case 1: Roentgenogram of the left shoulder, taken June 30, 1932, just before radiation treatment. Note the marked destruction of the entire scapula, also the lateral end of the clavicle and early erosion of the proximal portion of the lateral cortex of the humerus.

FIGS. 7 and 8.—Case 1: Roentgenograms showing the changes in the involved bones during and following the radiation treatment. Figure 7, taken July 16, 1932, 12 days after the beginning of the therapy; note that the mild erosion of the lateral cortex of the upper end of the humerus has definitely increased. Figure 8, taken August 29, 1932, shows progressive bone regeneration after the first course of radiation.

FIG. 9.—Case 1: Roentgenogram, taken November 19, 1938, showing the stationary condition of the regenerated bones.

appeared to be slightly pale, but was not suffering from acute discomfort. A large, diffuse swelling of the left shoulder was present involving the clavicular, supraclavicular, deltoid and scapular regions (Figs. 1 and 2). The tumor was hard in consistency, fixed, ill-defined and not tender. The overlying skin was diffusely red but not adherent.

The left axilla contained two firm, nodular, movable masses measuring 5 and 1.5 cm. in diameter, respectively. In the left lower cervical and supraclavicular regions, along the medial border of the tumor, were many firm lymph nodes, each about 2 cm. in diameter. The left shoulder joint could not be moved. Sensory changes in the left upper extremity could not be detected. Motion at the elbow and wrist was normal. Roentgenograms showed extensive destruction of the entire left scapula, marked destruction of the lateral end of the clavicle, and partial destruction of the upper end of the humerus (Fig. 6). Evidence of pulmonary, pleural or mediastinal metastasis was not present. Examination of other regions of the body was essentially negative. One of the enlarged lymph nodes in the left lower cervical region was removed and the histologic diagnosis was reported as lymphosarcoma (Fig. 5). The lesions in the bones were considered to be secondary in nature. Recently, at the suggestion of Dr. H. T. Kimm, this case was reviewed, and in the light of current knowledge concerning the subject herein dealt with, the diagnosis was changed to primary reticulum cell sarcoma of bone with metastasis in the regional lymph nodes.

On July 4, 1932, the tumor was observed to be considerably larger and several new masses, each about 2 cm. in diameter, were found in the subcutaneous tissue of the cervical and scapular regions on the right side. Examination of the blood showed 80 per cent hemoglobin (Sahli), and normal red, white, and differential counts. Abnormal leukocytes were not found. Weight 41.7 Kg. The blood Wassermann reaction was negative. A test for the presence of Bence-Jones protein in the urine was not carried out.

A series of roentgen ray treatments were administered between July 7, and September 7, 1932 (Table I). The pain gradually disappeared and the swelling began to regress 12 days after the therapy was started. A roentgenogram taken at this time showed increased erosion at the surgical neck of the humerus (Fig. 7). On July 30, 1932, definite improvement of the involved bones with evidence of regeneration of bone was first observed roentgenologically. On August 5, 1932, the patient complained of dull pain in the left elbow. Examination showed enlargement of the left epitrochlear nodes and roentgenologic evidence of a small area of rarefaction in the lateral cortex near the distal end of the humerus; these lesions subsequently disappeared following roentgenotherapy (Table I, Port VI). On August 16, new tumor nodules appeared in the posterior inferior axillary and infrascapular regions on the left side. These nodules regressed completely after roentgenotherapy (Table I, Port VII).

The blood picture on repeated examinations remained satisfactory. Chemical analysis of the blood showed, on August 2, 10.9 mg. per cent of calcium, 6.1 mg. per cent of phosphorus, and 0.42 and 0.72 units of phosphatase in two different specimens; on August 23, 11.4 mg. per cent of calcium, 4.3 mg. per cent of phosphorus; and on August 29, 11.4 mg. per cent of calcium and 4.0 mg. per cent of phosphorus.

The therapy produced progressive regression of all the lesions and by September 20, 1932, complete regression of the tumefaction had occurred with the exception of the anterior axillary mass which was then 3 cm. in diameter and of a small firm node in the left supraclavicular region. Repeated roentgenologic examinations showed progressive reossification of the involved bones (Fig. 8).

Between December 30, 1932, and January 23, 1933, a second series of roentgen ray treatments were administered through two fields in the left shoulder and one field in the left cervical region (Table II). The general condition remained satisfactory, and on February 14, 1933, the patient's weight had increased to 45.8 Kg. On May 16, 1933, the residual mass in the left anterior axillary region was noted to have become larger. Fifteen seeds of 0.3 Mm. Au. in wall thickness, each containing 1.16 mc. of radon, were inserted around this nodule; five seeds of 1.25 mc. each were inserted into the left supraclavicular space (June 20, 1933). A biopsy secured at this time from the axillary mass, by means of a Hoffman's punch, did not show the presence of tumor.

Subsequently, the patient has been examined from time to time. There has been no evidence of recurrence or metastasis of the tumor. The small nodule in the left

axilla has been stationary, apparently consisting of a mass of fibrous tissues (Figs. 3 and 4). The muscles of the shoulder have become atrophic and the motion of the joint limited. The left arm can be raised anteriorly to 90°, posteriorly to 45°, and in abduction to about 60°. The roentgenologic study on the occasion of the last visit, February, 1940, revealed the regenerated bones to be in good condition (Fig. 9). The patient is in apparently perfect health seven years and seven months after the institution of treatment.

PLATE III.

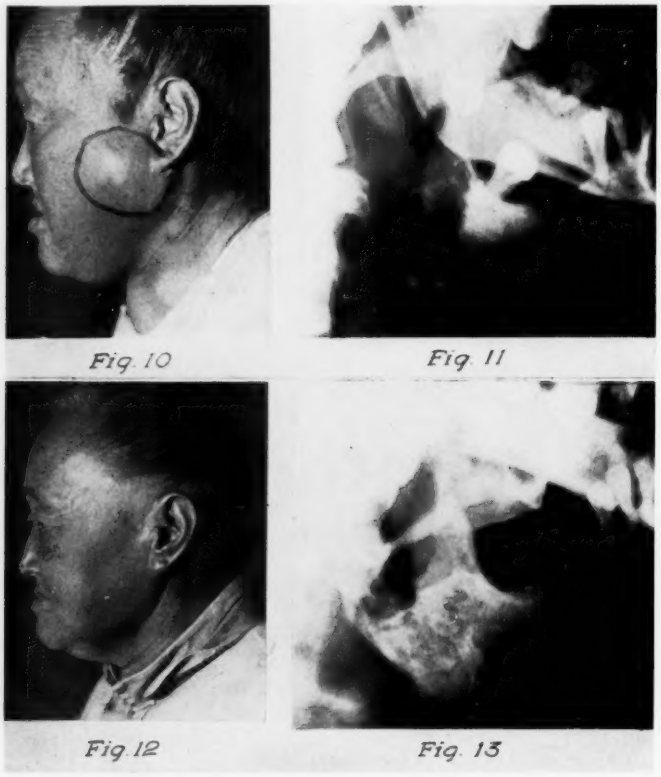


FIG. 10.—Case 2: Appearance of the tumor before treatment.
FIG. 11.—Case 2: Roentgenogram of the mandible before treatment. Note the marked destruction of the ramus. The condyloid process cannot be visualized.
FIG. 12.—Case 2: Normal appearance of mandibular region one month following radiation treatment.
FIG. 13.—Case 2: Roentgenograms of the mandible seven months following radiation treatment. Note the regeneration of the destroyed ramus.

Case 2.—A Chinese housewife, age 59, was first seen in the Surgical Clinic of the P.U.M.C. Hospital, June 18, 1938, complaining of a swelling in the left preauricular region for three months, and local pain in the same area for two months. The pain was dragging or burning in character and occurred only occasionally. During the previous month, the patient had experienced numbness in the left half of the lower lip. Trismus or dysphagia was not present. There was no history of nasal obstruction or bleeding. The general health was not affected by the present illness. Five years previously the patient had suffered from "toothache" for which most of her teeth had been extracted. There had been an area of swelling in the thyroid region since the age of 16.

Physical Examination.—The patient was well developed, well nourished and did not appear ill. The face was asymmetric due to the presence of a round, firm swelling,

TABLE I

ROENTGENOTHERAPY

Case 1: First Series

Date 1932	Dosage in r to Port*						
	I	II	III	IV	V	VI	VII
July 7	56						
8		40					
9	40						
11		40					
12	40						
13		40					
14	40	40					
15	40	40	132	132			
16	40	40					
18	40	40	132	132			
19	40	40					
20	40	40	132	132			
21	40	40					
22	80	80	132	132			
23	80	80					
25	80	80	132	132			
26	80	80					
27	80	80	132	132			
28	80	80			160		
29	80	80	132	132			
30	80	80			160		
Aug. 1	120	120	172	172			
2	60	60			160		
3	60	60	132	132			
4	40	40					
5		40	88	88			
6		40			160	200	
8		80	110	110			
9		40			160	200	
10		40	88	88			
11		40			160	200	
12			88	88			
13					80	200	
16					120	200	
18						120	160
20						80	160
23						120	160
25						80	160
27						80	160
30							160
Sept. 1							160
3							80
6							120
7							80
Total	1,336	1,600	1,602	1,602	1,040	1,480	1,400
						Grand total:	10,060

Factors of therapy:

Voltage:	160 K.V.
Current:	10 M.A.
Filter:	56 Mm. oil
	0.25 Mm. Cu.
	1.5 Mm. Al.
Skin target distance:	50 cm.
Intensity:	23.7 r. per minute measured in air.

* Port I: Left shoulder and supraclavicular region, anterior.
Size: 15x20 cm.
Port II: Left shoulder and scapular region, posterior.
Size: 20x20 cm.
Port III: Right supraclavicular, cervical and supraspinous regions, anterior.
Size: 8x10 cm.
Port IV: Same as Port III, posterior.
Size: 10x12 cm.
Port V: Left cervical, lateral.
Size: 8x8 cm.
Port VII: Left middle back, posterior.
Size: 11x14 cm.

7 cm. in diameter, which was fixed to the ramus of the mandible on the left side (Fig. 10). It was slightly tender. The overlying skin appeared normal. There was an enlarged, firm but freely movable lymph node, 2 cm. in diameter, just behind the left angle of the mandible. Enlarged lymph nodes were not found elsewhere. Hypoesthesia was present in the left half of the lower lip. Inside the mouth, the area of swelling could neither be seen nor palpated. The uvula was deviated slightly to the right. The tonsils and the nasopharynx were normal to inspection and palpation. Many teeth were missing; the remaining few were dirty and carious. A benign goiter was present. The liver and spleen were not palpable. Mild hypertension existed. Examination of the blood showed 9.4 Gm. per cent of hemoglobin and normal cell counts. Abnormal leukocytes were not found. Other laboratory data were not obtained.

Roentgenograms revealed a marked destructive lesion in the left ramus of the mandible (Fig. 11). Tissue aspirated from the mass was thought questionably to be lympho-epithelioma. When the case was restudied recently, the diagnosis of reticulum cell sarcoma seemed evident (Figs. 14 and 15).

TABLE II

ROENTGENOTHERAPY

Case 1: Second Series

Date	Dosage in r. to Port* I	II	III	K.V.†
Dec. 30, 1932	208	208	208	160
Jan. 3, 1933	208	208	208	"
5	208	208	208	180
7	208	208	208	"
9	208	208	208	"
13	156	156	156	"
16	104	104	104	"
18	78	78	78	"
20	52	52	52	"
28	104	104	104	"
Total	1,534	1,534	1,534	

* Port I: Left shoulder, axilla and supraclavicular region, anterior.
Size: 12x16 cm.
Port II: Left shoulder and scapula.
Size: 20x20 cm.
Port III: Left cervical region.
Size: 9x10 cm.

† The factors were the same as in the first series (Table I).

Daily roentgen ray treatments were started on July 11, 1938, using a large field which included the mandible as well as the entire cervical region on the left side. Later, the field was reduced and the radiation confined to the tumor and its immediately adjacent tissues (Table III). A total dose of 4,481 r was delivered in 49 days. The pain disappeared and the tumor began to regress rapidly one week after the treatment was started. By the end of the treatment, on August 29, 1938, the tumor had disappeared completely (Fig. 12). The enlarged lymph node in the left upper cervical region disappeared three weeks later. The skin tolerated the therapy well. In September, 1938, roentgenologic examination revealed that the lesion in the mandible had improved markedly. This change was progressive, as demonstrated at another roentgenologic examination on April 17, 1939 (Fig. 13). The last examination, on April 24, 1940, showed no evidence of local recurrence or metastasis. The function of the lower jaw was normal. The patient is in good health and has no complaint.

Discussion.—According to Parker and Jackson, 77 per cent of all cases of primary reticulum cell sarcoma of bone occur in patients under the age of

40, and 35 per cent under the age of 20 years, although any age-group may be affected. The disease usually occurs in the long or flat bones. The onset is similar to that of osteogenic sarcoma but the subsequent course differs greatly. The most common initial symptom is pain unrelieved by rest and

PLATE IV.

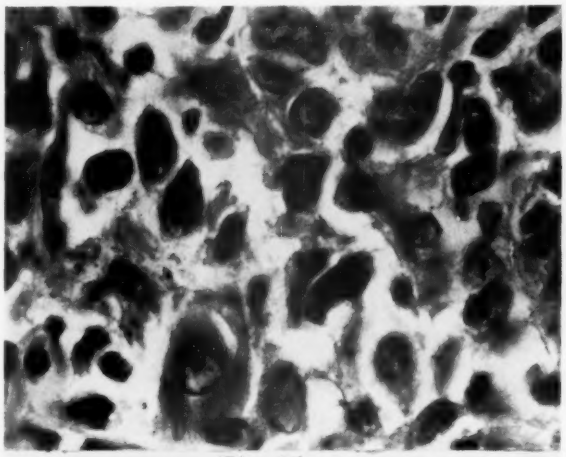


Fig. 14

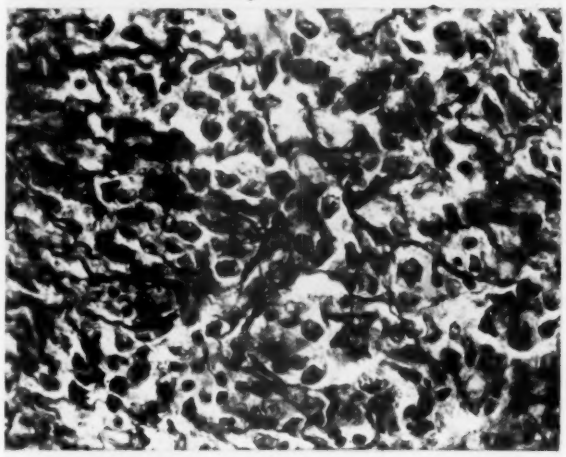


Fig. 15

FIG. 14.—Case 2: Photomicrograph of the tissue aspirated from the mandibular tumor before treatment, showing reticulum cell sarcoma. Hematoxylin-eosin stain. (×1,370)
FIG. 15.—Case 2: Photomicrograph of the same tissue shown in Figure 14. Foot's silver stain for reticulum. (×567)

localized at the site of the primary lesion or referred to the adjacent joint. Sometimes a painless swelling may be the first complaint. Not infrequently a pathologic fracture occurs before treatment is sought. In the majority of cases, tumefaction of the affected part is present at the time the patient is

first seen. The tumor may grow very rapidly and attain considerable size, involving the surrounding soft tissues. Metastasis occurs comparatively late and usually affects the regional lymph nodes rather than the lungs. Metastasis to bones occurs but infrequently. These characteristics are in contradistinction to the generalized spread which usually occurs relatively early in the course of reticulum cell sarcoma of the soft tissues.

While the lesion appears locally extensive and highly malignant, it seldom affects the general condition of the patient as does osteogenic sarcoma, and

TABLE III

ROENTGENOTHERAPY

Case 2

Date 1938	Dosage in r to Port* I	Date 1938	Dosage in r. to Port† II
July 11	102	Aug. 3	145
12	102	4	145
13	102	5	145
14	122	9	145
15	122	10	145
16	122	11	145
18	122	12	145
19	122	15	145
20	122	16	170
21	122	20	145
22	122	22	145
25	122	23	145
26	122	24	145
27	122	25	145
28	122	26	145
29	122	29	145
Aug. 1	122		
2	122		
3	122		
Total	2,136	Total	2,345
		Grand total:	4,481

Factors of therapy:

Voltage:	180 K.V.
Current:	8 M.A.
Filter:	56 Mm. oil
	0.5 Mm. Cu.
	2.0 Mm. Al.
Skin target distance:	50 cm.
Intensity:	17 r. per minute.

* Port I: Left half of mandible and entire left cervical region, lateral.
Size: 20x16 cm.

† Port II: Posterior half of body and entire ramus of mandible and the upper cervical region, lateral.
Size: 10x10 cm.

it is amenable to appropriate treatment. The roentgenographic appearance of the lesion is not characteristic. In the early stages, only mottled areas of destruction in the medulla may be observed. In more advanced cases marked osteolysis and rarely osteogenesis can be seen. Histologically, the structure is identical with that of reticulum cell sarcoma of a lymph node or other soft part.

Among primary bone lesions, reticulum cell sarcoma should be differentiated from Hodgkin's disease, lymphosarcoma, Ewing's sarcoma, osteogenic sarcoma, and osteomyelitis. As pointed out by Parker and Jackson, the histologic picture usually is sufficient for differentiation; in doubtful cases the clinical course will lead to the correct interpretation. Primary Hodgkin's disease and true lymphocytoma of bone are extremely uncommon. Osteogenic sarcoma and osteomyelitis do not respond favorably to radiation therapy.

We believe that the cases described herein fulfill the criteria outlined by Parker and Jackson. In the first one, since only a cervical lymph node was secured for histologic examination, the diagnosis of primary reticulum cell sarcoma of the scapula may be questioned. However, the favorable clinical course following treatment, the localization of the growth and the lack of evidence suggesting the presence of a primary lesion elsewhere, all indicate that this was a primary lesion of bone. It would be most improbable that an unrecognized primary lesion, if there had been such, would have remained concealed for more than seven years after the lesion in the scapula had been controlled by radiation.

Parker and Jackson found that early amputation followed by radiation of the adjacent lymph nodes yielded the best results. Three of their cases were treated by radiation alone. One of these patients died of the disease within two years and the other two were living for one and three years respectively, with the disease unchecked. In three other cases initial radiation was administered but, due to either local recurrence or metastasis to lymph nodes, subsequent amputation was performed. These patients were living and apparently well ten to 14 years later. The details of the radiation were not given. These data appear to show that radiation alone does not constitute effective treatment.

The results of irradiation in our cases, on the other hand, were distinctly encouraging. In both instances, the primary as well as the secondary lesions exhibited marked radiosensitivity, and complete regeneration of bone ensued after the disappearance of the tumor. The first patient is living and well, apparently free from the disease, seven years and seven months, and the second patient one year and eight months, after the treatment was completed. In our first case, there could have been no other choice of therapeutic measure, as the lesion was so extensive and so located that even the most radical surgical procedure could not have eradicated the disease. In the second case, hemisection of the mandible and wide removal of the neighboring soft tissues as well as of the cervical lymphatics could have been considered. However, we believe that in the management of such radiosensitive lesions, irradiation rather than surgery is the method of choice. For lesions of the long bones, amputation may yield equally good results. On the other hand, even in such instances radiation may be tried first without harm. In the three cases reported by Parker and Jackson in which radiation failed to arrest the disease, subsequent surgical attack effected an eventual cure.

first seen. The tumor may grow very rapidly and attain considerable size, involving the surrounding soft tissues. Metastasis occurs comparatively late and usually affects the regional lymph nodes rather than the lungs. Metastasis to bones occurs but infrequently. These characteristics are in contradistinction to the generalized spread which usually occurs relatively early in the course of reticulum cell sarcoma of the soft tissues.

While the lesion appears locally extensive and highly malignant, it seldom affects the general condition of the patient as does osteogenic sarcoma, and

TABLE III

ROENTGENOTHERAPY

Case 2

Date 1938	Dosage in r to Port* I	Date 1938	Dosage in r. to Port† II
July 11	102	Aug. 3	145
12	102	4	145
13	102	5	145
14	122	9	145
15	122	10	145
16	122	11	145
18	122	12	145
19	122	15	145
20	122	16	170
21	122	20	145
22	122	22	145
25	122	23	145
26	122	24	145
27	122	25	145
28	122	26	145
29	122	29	145
Aug. 1	122		
2	122		
3	122		
Total	2,136	Total	2,345
		Grand total:	4,481

Factors of therapy:

Voltage:	180 K.V.
Current:	8 M.A.
Filter:	56 Mm. oil
	0.5 Mm. Cu.
	2.0 Mm. Al.
Skin target distance:	50 cm.
Intensity:	17 r. per minute.

* Port I: Left half of mandible and entire left cervical region, lateral.
Size: 20x16 cm.

† Port II: Posterior half of body and entire ramus of mandible and the upper cervical region, lateral.
Size: 10x10 cm.

it is amenable to appropriate treatment. The roentgenographic appearance of the lesion is not characteristic. In the early stages, only mottled areas of destruction in the medulla may be observed. In more advanced cases marked osteolysis and rarely osteogenesis can be seen. Histologically, the structure is identical with that of reticulum cell sarcoma of a lymph node or other soft part.

Among primary bone lesions, reticulum cell sarcoma should be differentiated from Hodgkin's disease, lymphosarcoma, Ewing's sarcoma, osteogenic sarcoma, and osteomyelitis. As pointed out by Parker and Jackson, the histologic picture usually is sufficient for differentiation; in doubtful cases the clinical course will lead to the correct interpretation. Primary Hodgkin's disease and true lymphocytoma of bone are extremely uncommon. Osteogenic sarcoma and osteomyelitis do not respond favorably to radiation therapy.

We believe that the cases described herein fulfill the criteria outlined by Parker and Jackson. In the first one, since only a cervical lymph node was secured for histologic examination, the diagnosis of primary reticulum cell sarcoma of the scapula may be questioned. However, the favorable clinical course following treatment, the localization of the growth and the lack of evidence suggesting the presence of a primary lesion elsewhere, all indicate that this was a primary lesion of bone. It would be most improbable that an unrecognized primary lesion, if there had been such, would have remained concealed for more than seven years after the lesion in the scapula had been controlled by radiation.

Parker and Jackson found that early amputation followed by radiation of the adjacent lymph nodes yielded the best results. Three of their cases were treated by radiation alone. One of these patients died of the disease within two years and the other two were living for one and three years respectively, with the disease unchecked. In three other cases initial radiation was administered but, due to either local recurrence or metastasis to lymph nodes, subsequent amputation was performed. These patients were living and apparently well ten to 14 years later. The details of the radiation were not given. These data appear to show that radiation alone does not constitute effective treatment.

The results of irradiation in our cases, on the other hand, were distinctly encouraging. In both instances, the primary as well as the secondary lesions exhibited marked radiosensitivity, and complete regeneration of bone ensued after the disappearance of the tumor. The first patient is living and well, apparently free from the disease, seven years and seven months, and the second patient one year and eight months, after the treatment was completed. In our first case, there could have been no other choice of therapeutic measure, as the lesion was so extensive and so located that even the most radical surgical procedure could not have eradicated the disease. In the second case, hemisection of the mandible and wide removal of the neighboring soft tissues as well as of the cervical lymphatics could have been considered. However, we believe that in the management of such radiosensitive lesions, irradiation rather than surgery is the method of choice. For lesions of the long bones, amputation may yield equally good results. On the other hand, even in such instances radiation may be tried first without harm. In the three cases reported by Parker and Jackson in which radiation failed to arrest the disease, subsequent surgical attack effected an eventual cure.

The success of irradiation may depend primarily on the method of application. In general, protracted, fractionated radiation is preferred with the total dosage brought up to the maximum, according to the size, location and distribution of the given lesion. In our cases, a total dose of 4,000 to 5,000 r. was delivered to the primary lesion, and 1,500 to 3,500 r. to each of the metastatic lesions.

It is interesting to note the remarkable regeneration of the involved bones following irradiation. In the first case, the entire scapula had been destroyed and fragmented by the infiltrating tumor, its normal contour being lost completely (Fig. 6). During the first two weeks of irradiation, there seemed to be even more decalcification or osteolysis (Fig. 7). Reossification began in about three weeks and thereafter progressed steadily (Fig. 8), even after the completion of the therapy. Complete regeneration occurred within a period of six to seven months, the scapula as well as the clavicle and the humerus resuming normal structural contour (Fig. 9). Likewise, in the second case, the destroyed portion of the mandible regenerated following radiation (Figs. 11 and 13). The mechanism of regeneration or reossification following irradiation of bone tumors is an interesting phenomenon. Baunschwig's[1] work on the repair of bone following irradiation in benign giant cell tumor is illuminating. But in cellular tumors, such as reticulum cell sarcoma in which the bone as well as the surrounding soft tissues are extensively destroyed, metaplasia within the tumor due to irradiation does not seem likely to play the principal rôle. The endosteal and periosteal elements also must suffer severe damage, and how their activity can be restored to reform a perfect bone is difficult to explain. It may be assumed, however, that the periosteum is not totally destroyed and that regeneration originates from this structure.

SUMMARY

Two cases of primary reticulum cell sarcoma of bone are presented.

The outstanding clinical features of the disease are: (1) An extensive local lesion which appears out of harmony with the usual good general condition of the patient; (2) a comparatively benign course in spite of the highly malignant appearance of the tumor; and (3) a high degree of radiosensitivity which renders the lesion amenable to appropriate treatment.

Radiation was the only form of therapy employed in the two cases herewith reported. The first patient is living and well seven years and seven months, and the second patient one year and eight months, following the institution of treatment.

In the first case, roentgenotherapy effected complete regeneration of an extensively destroyed scapula, and resulted in the preservation of a useful limb. In the second case, the involved mandible reossified with good functional result.

The authors wish to thank Dr. H. T. Kimm for his helpful suggestions in the preparation of this report.

REFERENCES

1 Brunschwig, A.: Observations on the Changes Occurring at Benign Giant Cell Tumor Sites Several Years Following Treatment by Conservative Measures. Am. Jour. Roentgenol., **40,** 817, 1938.

2 Craver, L. F., and Copeland, M. M.: Lymphosarcoma in Bone. Arch. Surg., **28,** 809, 1934.

3 Ewing, J.: A Review of the Classification of Bone Tumors. Bull. Am. Coll. Surgeons, **24,** 290, 1939.

4 Kuhns, J. G., *et al.*: Sixty-ninth Report of Progress in Orthopedic Surgery. Arch. Surg., **39,** 496, 1939.

5 Oberling, C.: Les réticulosarcomes et les réticuloendothéliosarcomes de la moelle osseuse (Sarcomes d'Ewing). Bull. Assoc. franç. p. l'étude du cancer, **17,** 259, 1938.

6 Parker, F., and Jackson, H.: Primary Reticulum Cell Sarcoma of Bone. Surg., Gynec., and Obstet., **68,** 45, 1939.

7 Simmons, C. C.: Bone Sarcoma—Factors Influencing the Prognosis. Surg., Gynec., and Obstet., **68,** 67, 1939.

UROLOGY AWARD

The American Urological Association offers an annual award 'not to exceed $500.00' for an essay (or essays) on the result of some specific clinical or laboratory research in Urology. The amount of the prize is based on the merits of the work presented, and if the Committee on Scientific Research deem none of the offerings worthy, no award will be made. Competitors shall be limited to Residents in Urology in recognized hospitals and to urologists who have been in such specific practice for not more than five years.

Essays shall be in the hands of the Secretary, Dr. Clyde L. Deming, 789 Howard Avenue, New Haven, Conn., on or before April 1, 1942.

PERIPHERAL ARTERIOSCLEROSIS

NATHANIEL C. SCHLOSSMANN, M.D.*
NEW YORK, N. Y.
AND
LEON GERBER, M.D.
WASHINGTON, D. C.
FROM THE LABORATORIES OF THE MOUNT SINAI HOSPITAL, NEW YORK CITY, N. Y.

A REINTERPRETATION of morphologic changes in sclerotic vessels of the coronary tree substantially altering the concepts of the mechanism of coronary occlusion stimulated our study in peripheral vascular arteriosclerosis. Patterson,[1, 2] Wartman,[3] Winternitz, Thomas and Le Compte,[4] Leary,[5] and Horn and Finklestein[6] showed that hemorrhage into the intimal plaque in the coronary artery was a significant etiologic factor in occlusion of the lumen occurring as the most frequent of all precipitating events. Previous to Patterson's work in 1936, intimal hemorrhage had been noted, but its clinicopathologic relationships were overlooked.[7, 21, 22] The cause of peripheral vascular occlusion, exclusive of embolus, was thought to be either the gradual compromise of the lumen by an encroaching plaque or the thrombus formation upon a fatty or hyperplastic plaque in that portion of the vascular tree where arteriosclerotic changes were so frequent that reduced blood velocity and ischemic endothelium set the stage for platelet and fibrin deposition.[48]

We surveyed the arteriosclerotic peripheral vessels found in 74 amputated lower extremities to determine the series of events within the vessel wall culminating in occlusion. The specimens amputated because of peripheral, uncontrolled gangrene, and collected as routine surgical material over a period of three years, were examined to determine the frequency of all of the causative mechanisms of the peripheral vascular occlusion. The material was analyzed to evaluate the influence, if any, of diabetes mellitus upon the mechanisms of occlusion in the peripheral vessels. The technic of controlled trypsin digestion was undertaken to establish the nature of fibrinoid substance and to determine the state of the stroma within the atheroma. The importance of hemorrhage within the intima of the arteriosclerotic vessels brought up questions concerning the fate of the subendothelial plaque. These issues will be discussed in order to demonstrate the orderly events in the vessel wall in peripheral vascular arteriosclerosis which lead finally to the catastrophic thrombosis.

METHODS AND MATERIAL.—Seventy-four lower extremities were received as surgical specimens after amputation for peripheral gangrene associated with either diabetes or arteriosclerosis. The vascular tree was removed *en masse* with a minimum of trauma and immediately fixed in 20 per cent formalin. The vessels were rapidly decalcified and sectioned in serial fashion

* Theodore Escherich, Fellow in Pathology.

at intervals of 1–3 Mm. Each section was examined macroscopically. Those which presented the gross findings of luminal occlusion were studied histologically. Hematoxylin and eosin were used as the routine stain. Weigert's Elastica, van Gieson and Mallory-Azan connective tissue stains, Bielschowsky's silver impregnation, Sudan III stain for fat on both simple and gelatin frozen-section, the Lepehne preparation for hemoglobin and the iron stain for blood pigment were employed wherever indicated.

Particular attention was paid to that part of the vessel which showed the most recent change. Patent segments of vessels proximal to the level of occlusion were studied to define the mural lesions which subsequently led to thrombosis. Macroscopic diagnosis of the nature of occlusion in each vessel was checked by histologic examination. Microscopic serial sections were made in ten instances to trace mural capillaries to their origin.

Trypsin digestion was used to determine the character of the stroma of the atheroma and to define the fibrinoid substance. This technic, described by Romeis[8] and modified for our purpose, consisted of placing the deparaffinized microscopic section in a saturated solution of trypsin at the p_H of seven to eight. A small amount of chloroform or tolulol was added in order to prevent bacterial growth. The digestion of blood elements and tissue took place in a sequential manner, *i.e.*, serum and nuclear protein, fibrin, blood platelets and the white blood cells were first consumed.[9] Red blood cells were the most resistant of all the blood elements. The interfibrillar ground substance disappeared before young connective tissue fibers. Completely necrotic collagen was somewhat more resistant than fibrin, but was digested before partially degenerated connective tissue. Adult healthy collagen remained after all other protein had been consumed, but eventually it too disappeared.

Pathogenesis of Intimal Changes which Lead to Occlusion.—For the purpose of our discussion the arteriosclerotic process in the peripheral artery shall be divided into two pathogenetic phases; (1) the etiologic insult; and (2) the reparative reaction to the damage.

The nature of the initial insult to the vessel wall has still been undetermined. The influence of the high fat diets of Saltykow,[10] Anitschkow,[11] and Leary[12] in producing experimental atherosclerosis must be reëxamined to determine their significance in view of the work of Aschoff[13] reviving the wear and tear concept of Virchow to show that the first detectable finding in the vessel is not a cholesterol impregnation in an otherwise healthy area, as the experimental atheromatoses in the rabbit would indicate, but rather that the primary lesion of arteriosclerosis occurs as a change in the interfibrillary ground substance. Aschoff has emphasized that the ground substance is a complicated colloidal-gel system in constant fluid equilibrium with itself. Whether this change represents physiologic senesence of connective tissue or the first step in arteriosclerosis is difficult to determine, and for our purposes is of no immediate import. The foregoing facts have been demonstrated by Lange,[16] and Leary[14] in young individuals succumbing to unrelated disease processes. In the aortas of the youths, barely visible, slightly raised, tan

streaks are found, running longitudinally on the posterior wall between the intercostal vessels, transversely in the sinuses of Valsalva and about the occluded ductus arteriosus. Histologically, the first change to be noticed in these "endothelial blisters," described in detail by Zinserling,[17] is a separation of the subendothelial structure of the intima by a finely granular, edematous pale material which does not take the stains for fat.[14] The substance is acellular and structureless. Aschoff has interpreted this change as an alteration of hydration of the colloidal-gel. Lange,[16] and Leary[14] termed the state one of "mucoid degeneration." Duff[15] noted a similar state in the media.

The nature and morphogenesis of the fat deposition has still remained unsolved.[16, 17] Anitschkow and the Russian school[11] definitely demonstrated by the fat feeding experiments in the rabbit that the lipids diffuse from the blood stream through intact endothelium toward the media. Winternitz[4] has suggested that the cholesterol is gathered from extravasated blood elements and serum infiltration, the so-called "exudative" or first phase in the pathogenesis of arteriosclerosis. As yet the significance of fat infiltration as to origin and fate in arteriosclerosis has not been unveiled. Its relation to the high fat dietary habit of man has been inconclusive despite Snapper's[18] remarks that in West China, where the habitual diet is low in fat, coronary occlusion has never been observed.

The second phase of the arteriosclerotic process is essentially the reparative response to the damage initiating in the ground substance and the cholesterol deposition.[6] The repair consists of capillary sprouting, fibroblastic proliferation and phagocytosis of the lipids, a typical nonspecific body reaction forming in the wall of the vessel a cellular, vascularized plaque of granulation tissue. The subsequent course depends upon the degree of capillary response which Leary[19] has demonstrated to be proportionate to the age of the patient. If the vascularization of the newly formed plaque is nutritiously adequate, the fat is entirely resorbed and collagen is laid down to form a hyperplastic scar. The fibroblasts growing into the damaged area roughly perpendicular to the long axis of the vessel lay down collagen in a pattern concentric with the lumen. As the connective tissue contracts, most of the capillary sprouts are cut off and the final picture of an avascular fibrous plaque manifests itself.

While the fibrotic plaque represents the most advantageous end-stage, another course of events ensues when the capillary proliferation is less pronounced. A state of tissue starvation results and eventually the entire area undergoes ischemic necrosis. In the well vascularized plaque of thriving granulation tissue, there is excessive fibroblastic activity and a minimum of free extracellular fat. In a poorly vascularized plaque, there is slight fibroblastic activity and excessive amounts of extracellular but noncrystallized fat deposited in a fine fibrillary framework. In a totally inadequately vascularized plaque, the fibroblasts are absent. Fat has crystallized on a necrotic structureless afibrillary stroma.[19] This final state represents the mature atheromatous abscess, an end-stage of atherosclerosis much less advantageous than the fibrotic plaque.

Further expression of the necrosis in the mature atheroma is the formation of calcium salts of the fats. The calcium salts appear first as microscopic granules scattered throughout the atheroma; later they coalesce to form large calcium plaques.

The formation of bone in the intima parallels the deposition of calcium. This type of osteogenesis is not the same as that which is found in the long bones of the body where obsteoblasts and a predisposing cartilaginous structure are of primary importance. Similar bone formation has been described by Allen[20] in breast tumors, where there was no preëxisting cartilage. Allen's statement that heterotopic ossification represents a differentiation in no way corresponding to the "concept of preformed cellular endowments" but rather is a manifestation of the dictates of environment, appears to apply to the human arterial wall, where cartilage is never seen, and osteoblasts are conspicuously absent. While capillaries are characteristically not frequent about areas of calcification, they are much more evident about the sites of secondary ossification, particularly where the marrow is differentiated. What the significance is of this observation, noted also by Horn and Finkelstein,[6] is as yet unknown. In any event, intimal petrification becomes another end-point in arteriosclerosis, representing a much less advantageous result of the reparative processes than the fibrotic plaque.

In the mature atheroma, it has been emphasized that the paucity of capillarization is the factor responsible for the end-stage of atheronecrosis. However, close inspection of the atheromatous abscess reveals that whatever vascular channels do exist are found at the periphery of the lesion and that the center of the atheroma only is devoid of capillaries. The integrity of the delicate wall of the capillary maintaining itself against the pressure of the blood stream depends upon the surrounding extravascular stroma. When the stroma undergoes necrosis, the support of the capillary disappears, rhexis of the wall follows, and a flooding of blood elements ensues into the atheromatous abscess. Our material showed that the athero-hematoma was as frequent in patent vessels as in the freshly occluded portion of the arterial tree. Factors, other than stromal necrosis, have been proposed in playing a rôle in the capillary rupture. Boyd[7] believes that the athero-hematoma represents an inflammatory reaction. Paterson[1] suggests that the rupture of the capillary is related to the variations in the pressure of the parent vessel from which the intimal capillary is derived. In the capillary of the peripheral vascular bed the tension of the blood flow is practically independent of the pressures of the large arteries because of the friction losses dissipated within the extensive peripheral bed. *Per contra,* the mural capillary, situated anatomically only a short distance from the main arterial lumen and in immediate communication with it, is completely dependent upon the changes in the blood pressure therein.

The location of the hemorrhagic atheroma within the intima is the etiologic important factor which governs the course of subsequent happenings. The occurrence of a small hemorrhage in a plaque which does not encroach upon the lumen eventuates only in scar tissue. The event of a small hemorrhage

in a plaque which already has severely compromised the lumen or of a massive hemorrhage in a mildly sclerotic vessel unaccompanied by endothelial destruction results in occlusion without thrombosis (Fig. 1). Here the swelling of the plaque assumes such proportions that the occlusion is entirely mechanical. Hemorrhage immediately beneath the endothelium in a necrotic fatty plaque is followed by luminal thrombosis in the majority of instances of recent occlusion (Fig. 2). Microscopic serial sections of athero-hematomata located beneath the fresh thrombus reveals that rupture of the plaque into the lumen is not always necessary for thrombus formation. The injurious effect of sudden

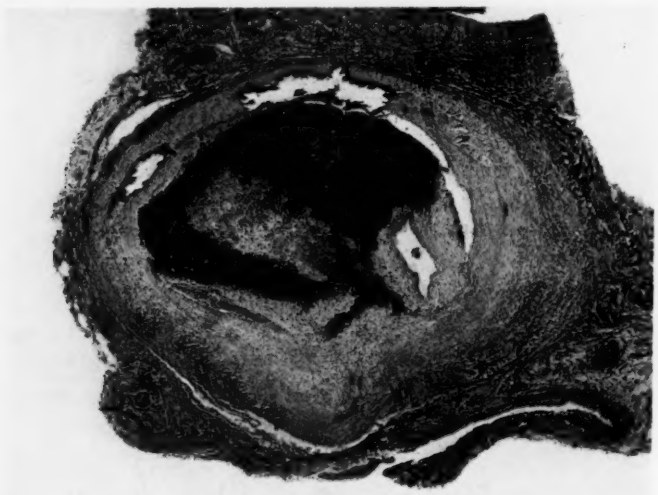
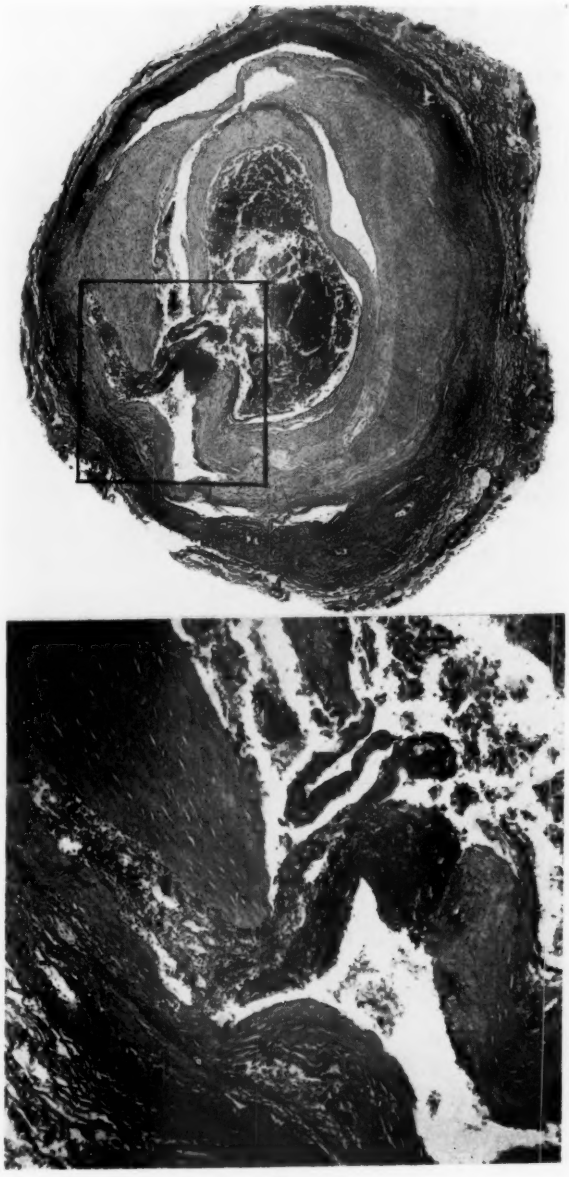


FIG. 1.—Massive hemorrhage into intimal fatty plaque, with compression occlusion of lumen. (×18)

swelling of the atheroma under the endothelium is sufficient to set the stage for platelet and fibrin deposition.[23]

The fibrotic plaque, described previously as an advantageous stage of healing, in time may arrive at a less desirable end. As the scar tissue contracts capillaries are choked off until ischemic changes occur. The collagen undergoes necrosis to form a completely avascular atheroma. The morphogenesis of necrotic stroma, fat deposition and subsequent calcification is in every way identical with primary atheromatous abscess. If this degeneration occurs close to the endothelium, the possibility of occlusion by similar mechanisms to those of the primary fatty plaque are evident. Occasionally the atheroma without the insult of hemorrhage precipitates thrombosis. If the enlarging fatty mass situated in the subendothelial stroma causes necrosis of the endothelium, thrombosis results upon the ragged overlying ulcer.[48] This mechanism of occlusion was particularly frequent in the specimens of arteriosclerotic thrombosis of the aorta which, relative to our subject of the mechanism of occlusions in the vascular tree, were also examined. In the peripheral artery, thrombosis upon the atheromatous ulcer was uncommon.

A



B

FIG. 2.—(A) Hemorrhage into intimal fatty plaque, with endothelial destruction and luminal thrombus. (×28). (B) Higher power photomicrograph of area outlined in Fig. 3a. (×100)

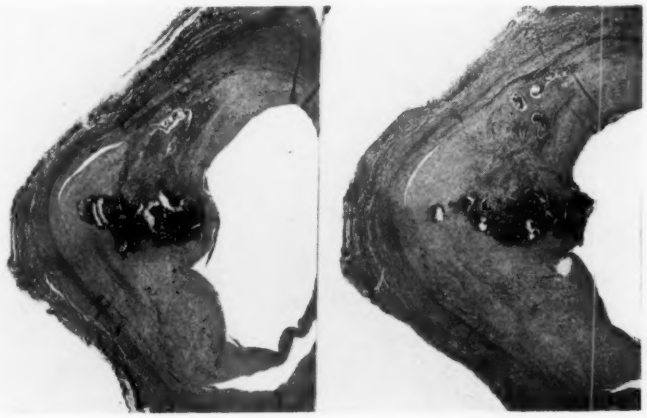
The fibrotic plaque undergoes ischemic changes at times in another direction. The connective tissue is converted into a state of degenerated collagen, assuming the properties of "fibrinoid" substance. If this reaction takes place immediately beneath the endothelium, associated ischemic changes of the endothelium lead to thrombus deposition.

Regardless of the nature of the arterial occlusion peripheral gangrene always mirrors a failure of the arterial perfusion. Since anastomotic arterial shunts in the lower extremity are extremely numerous even in the healthy state, massive damage to the arterial tree of the leg has to be inflicted before gangrene ensues. In all of our specimens, at least two out of the three large arteries of the leg are either occluded or severely encroached upon. This pathologic picture corroborates Veal's[24] arteriographic findings in intermittent claudication in legs of competent perfusion; one vessel is occluded in 50 per cent of cases; marked narrowing without obstruction is found in 13 per cent; and the remainder of the series shows many obliterated finer branches with patent large arteries. Likewise, in our specimens, multiple focal occlusions throughout the vascular tree were the rule. The usual picture was to find old fibrotic luminal occlusions in the distal segments of arteries while proximally either a recent thrombus or some other type of acute occlusion was manifest. In 15 specimens of this series, the only type of occlusion to be noted was fibrotic scar tissue. No recent thrombus was found. This situation occurred particularly in the limbs amputated at the level of the lower third of the leg. In the same group, specimens of reamputation also occurred. Our subsequent statistics on the categories of vascular occlusion are affected by these facts. The group of acute closures is conceivably too low, the frequency of old healed thrombi too great because the presence of an acute vascular accident proximal to the level of amputation was not ruled out. The fact that the surgical stump healed at a level below which no recent occlusion was found was of no import in the exclusion of a fresh luminal thrombus above the site of amputation.

Types of Vascular Occlusion.—By analysis of our material there was established definite morphologic evidence leading to peripheral vascular occlusion. The appended grouping and Table I comprised the categories of lesions within the arterial tree which reduced perfusion to such a level that peripheral gangrene followed.

Group I. Thrombosis secondary to hemorrhage.
Group II. Thrombosis upon a plaque.
Group III. Massive hematoma of the wall.
Group IV. Arteriosclerosis with:
(1) Severe luminal encroachment.
(2) Narrowing and thrombosis.
(3) Mural hemorrhage.
(4) Hemorrhage and thrombosis.
Group V. Granulation tissue.

We were guided by several principles in determining into which category each of our specimens belonged. The most recent proximal occluding lesion was always regarded as the precipitating cause of the peripheral gangrene. The presence of extensive arteriosclerosis with luminal encroachment or old organized distal occlusions was relegated to secondary importance in the



(a) (b)

FIG. 3.—(a) Intact atheromatous abscess in intimal hyperplastic plaque, with small parietal overlying thrombus. (×17) (b) Same lesion as in Fig. 4a, at level of ulceration into lumen, with seepage of blood elements into subendothelial portions of plaque. (×15)

presence of recent proximal thrombosis. The latter was the imminent factor in the process of the peripheral gangrene; before this, the impairment of circulation by previous insults was not severe enough to cause necrosis. When no acute lesion was found, old fibrotic organized occlusions were considered of greater import than severe arteriosclerosis with narrowing of the lumen. In Group IV, where the primary occluding mechanism was the excessive arterio-

TABLE I

MECHANISMS OF PERIPHERAL VASCULAR OCCLUSION

Group		No. of Specimens	Percentage
I.	Thrombosis secondary to hemorrhage	36	49%
II.	Thrombosis upon a plaque	5	7%
III.	Massive hematoma of the wall	1	1%
IV. 1.	Arteriosclerosis with severe luminal encroachment	11	15%
2.	Arteriosclerosis with narrowing and thrombosis	1	1%
3.	Arteriosclerosis with mural hemorrhage	4	5%
4.	Arteriosclerosis with hemorrhage and thrombosis	1	1%
V.	Granulation tissue	15	20%
	Total number of specimens	74	

sclerotic proliferation with great reduction of luminal size, the occurrence of acute mural hemorrhage and/or fresh thrombosis in the pin point lumen was regarded as a mere coincidental event.

GROUP I—*Occlusion by Thrombosis with Intimal Hemorrhage.*—Thrombosis upon intimal athero-hematoma constituted the nature of occlusion of the largest group of our cases. The lesion was found in 36 (49 per cent) specimens. The thrombus varied from the typical picture of layered platelet and

fibrin deposition with the other formed blood elements caught in the interstices to the more organized states of capillary sprouting, cellular infiltration and fibroblastic proliferation. Beneath the thrombus the endothelium was either disrupted or intact. If the athero-hematoma occurred immediately under the endothelium, an actual dehisence of the latter resulted; the hemorrhages of the mural plaque broke into the blood stream, and thrombosis eventuated on the necrotic and hemorrhagic mural ulcer (Fig. 2). However, if the hemorrhage took place deep in the intima, the endothelium was found intact despite thrombosis. This fact was established only after serial sections were made through the entire length of the atheroma. In these specimens, the swelling of the atheroma by the blood elements seemed to have damaged the endothelium sufficiently to precipitate thrombus formation.[23]

In order to determine the source of the intimal hemorrhage, study of the atheromatous abscess was pertinent. In the intact early (immature) atheroma, the stroma was fibrillary, relatively healthy connective tissue. Large amounts of uncrystallized lipids existed in the interstices. Many capillaries, frequently dilated, coursed through the lesion. The framework had the staining characteristics of healthy collagen. At the periphery, the fibrillary stroma gradually blended into the surrounding dense connective tissue.

In the advanced (mature) atheroma the fibrillary framework was replaced by structureless, smudgy acellular mass. Cholesterol crystals were deposited in acicular fashion. The connective tissue stains revealed that the collagenous stroma was in a state of advanced necrosis.[5, 12] Sudan III shows an intensive accumulation of fat in noncrystalline as in the crystalline state. Trypsin rapidly digested this necrotic mass leaving behind the encircling healthy capsule. At the periphery of the atheroma there was a characteristic separation of collagen fibers to fray as individual strands and dangle freely in the atheroma. Though relatively infrequent, capillaries extended from the capsule of the lesion into the necrotic plaque. Whereas the integrity of the capillary wall depended for support on the surrounding stroma, the necrotic state of the latter assumed singular import in the rhexis of the delicate walls of the former. Thus, the mechanism of mural athero-hematoma became evident.

GROUP II—*Occlusion by Thrombosis without Intimal Hemorrhage.*—Thrombosis upon an intimal plaque without hematoma was found five times (seven per cent) in our series. In past years, this mechanism of occlusion had erroneously been believed to be most frequent.[6]

Many have observed that it was impossible to produce experimental thrombosis of either artery or vein without damaging the endothelium.[23, 25] In arteriosclerosis the subendothelial connective tissue mirrored the health of the endothelium. In each instance of thrombosis upon an intimal plaque there was extensive degenerative lesions beneath the thrombus formation. In one case, where an atheromatous abscess was found immediately under the endothelium, the necrosis of the stroma so compromised the endothelium that rhexis resulted. In Figure 3 a, a parietal thrombus has formed over the mural necrotic fatty avascular plaque. In Figure 3 b, the plaque has broken

through the endothelium; fibrin and serum have infiltrated into the subendothelial zone which assumes an azure character distinct from the brighter red necrotic stroma deeper in the lesion. Trypsin digested the fibrin and serum proteins to leave the uniform homogeneous necrotic framework of the atheroma.

The other specimens which presented thrombosis upon plaques without intimal hemorrhage manifested a different status of degeneration in the underlying arteriosclerosis. Beneath the endothelium the degenerative "fibrinoid" change was noted in the sclerotic plaque. This degeneration, first described by Neumann,[26] appeared homogeneous, smudgy, acellular and intensely red in the routine hematoxylin and eosin preparation. Tinctorially, fibrinoid substance duplicated all the properties of fibrin to such an extent that some workers[22, 27, 28, 29] believed both substances to be identical. Others[30, 31] postulated that the fibrinoid appearance of collagen was due to a splitting of the connective tissue into its component fibrils, with seepage of fibrin into the interfibrillar spaces. Trypsin digestion definitely differentiated fibrinoid substance from fibrin. In controlled digestion the fibrin and cellular elements of the thrombus disappeared while the fibrinoid matter remained untouched. Connective tissue stains revealed the same separation, fraying and dangling of healthy collagen fibers at the edge of this substance that was found at the periphery of the atheroma. Moreover, trypsin digestion differentiated fibrinoid substance from the necrotic stroma of the atheroma, for after exercising extreme care in controlling the digestion we found that the atheromatous framework was consumed before the fibrinoid material was touched. The fibrinoid substance, in turn, was digested before healthy collagen was altered. With this differential digestion, we separated the fibrinoid change from true fibrin, and entertained the thought the fibrinoid change was an alteration in the state of collagen. A more detailed account of this phase of arteriosclerosis will be dealt with in a forthcoming publication.

Group III—*Occlusion by Plaque due to Intimal Hemorrhage.*—The encroachment upon the lumen by intimal athero-hematoma to such a degree that circulatory insufficiency resulted comprised a small but extremely significant group of our specimens (Fig. 1). In one instance, this lesion accounted for the closure of the popliteal artery and was the significant factor in producing the peripheral gangrene. In three other instances massive athero-hematomata were also responsible for occlusion, but since, at more proximal levels, thrombus formation within the lumen was associated with the same catastrophe, these specimens were classified elsewhere. In a host of other sections recent mural athero-hematomata without encroachment of the lumen were found. The common occurrence of the mural hemorrhage in the patent portion of the arterial tree, as well as in the more distal occluded areas, tended to establish the mural lesion as a forerunner of thrombosis (Fig. 4.). If mural hemorrhage occurred without luminal obstruction, no decrease of circulatory perfusion resulted. In the instances where intimal athero-hematoma occurred without endothelial compromise or rupture, occlusion resulted when encroachment upon the lumen was complete. The pathogenetic import of mural hem-

orrhage within the larger group in which arterial thrombosis followed the athero-hematoma became apparent from the study of this smaller group of specimens. The thrombus occurred only as a sequela of the hemorrhage chronologically happening later in the processes of arterial occlusion as a catastrophic end-stage.

GROUP IV—*Occlusion by Extensive Arteriosclerosis.*—Severe arteriosclerosis, morphologically delineated by all of the changes noted in the advanced state,[32, 33] and functionally associated with extreme reduction in luminal size, was found in 17 (23 per cent) specimens. In 11 instances, the patent lumen

FIG. 4.—Hemorrhage in a massive atheromatous abscess, occurring as an incidental finding in the femoral artery proximal to occlusion of the popliteal artery by thrombosis which was secondary to mural athero-hematoma.

was traced throughout all of the sections. Blumgart, Schlesinger and Zoll,[34] and Friedberg and Horn[36] renewed interest in a comparable condition within the heart, the state of coronary insufficiency or failure. They found that the incompetency of myocardial perfusion associated with the severe arteriosclerosis and luminal narrowing resulted in subendocardial myomalacia, a comparable condition to the distal phalangeal gangrene characterizing our specimens in which severe arteriosclerosis occurred. Whereas it was beyond the scope of this discussion to enumerate the dynamic factors brought into play in the precipitation of the gangrene, this subject has been discussed in detail by Friedberg and Horn[36] in its relationship to the coronary tree, and by Hines and Barker[35] in the peripheral arteries.

Coincidental to the extensive arteriosclerosis, a thrombotic obliteration within a pin point-sized lumen was found in one instance. Fresh subendothelial hemorrhage occurring five times was the precursor of a luminal thrombosis in one specimen.

It must be emphasized that despite the fact that the arterial tree possessed no actual occlusion in the 11 specimens of arteriosclerosis with narrowing of

the lumen we realized that a thrombotic process might have been located above the level of amputation. The fact that the stumps subsequently healed did not fully rule out this possibility.

GROUP V—*Occlusion by Granulation Tissue.*—In 15 (20 per cent) specimens the lumen was completely obliterated by fibrotic scar tissue. It was impossible, microscopically, to differentiate the vascular channels as to whether

FIG. 5.—Recent hemorrhage into old granulation tissue occlusion. (×29)

they represented recanalizing capillaries or residua of the original lumen. Moreover, it was impossible to determine through what mechanism the scar obliterating the lumen originated and what end-stage it represented.[4, 6] The collagen pattern was unrevealing. The presence of iron pigment was of no help, for both intimal hematoma and luminal thrombus leave the same residue. The presence of subendothelial elastic fibers was of little aid. They were not infrequently observed about recanalized channels as well as the true lumen. Horn and Finklestein,[6] and von Glahn[37] noted a similarly confusing state in vessels of the coronary tree.

In the old fibrotic occluded vessel, a frequent finding was that of secondary atheromatous abscess and fresh hemorrhage with the luminal scar (Fig. 5.). When a state of ischemia resulted within the organizing thrombosis, the atheroma was formed. As it underwent necrosis, capillary rhexis and hemorrhage resulted.

Diabetes.—No specific effects of diabetes mellitus were noted in any specimen upon the pathologic events within the arterial tree resulting in peripheral gangrene. We were unable to distinguish any unique morbid features in the diabetic vessels. Eliason and Wright[49] found that 55 per cent of the cases of senile gangrene of the lower extremities were diabetic. In our series of 74 specimens, 35 (44 per cent) were diabetic. In Table II, we subdivided the

mechanisms of arterial occlusion into diabetic and nondiabetic categories. Outside of the fact that all five instances of thrombosis upon a plaque fell into the nondiabetic group, no significant difference was evident.

TABLE II

MECHANISMS OF ARTERIAL OCCLUSION IN DIABETIC AND NONDIABETIC CATEGORIES

	Thrombosis upon Hemorrhage	Thrombosis upon Plaque	Mural Hematoma	Severe Arteriosclerosis	Granulation Tissue
Diabetic.....	19	0	1	7	8
Nondiabetic.....	17	5	0	10	7

Mural Vascular Tree.—The vascular supply to the arterial tree brought up many questions which have yet been unanswered. In the healthy vessel, the presence of mural capillarization has remained a matter of dispute. In the intima, capillaries have not been found. Although Winternitz and his coworkers [4, 38] demonstrated an arborizing network in the intima of the aorta of a healthy cow by subendothelial perfusion of India ink at the tremendously high pressures of 500 to 1,000 Mm. of mercury, this has never been duplicated in normal human vessels. These capillaries were demonstrated in the intima of the bovine aorta in order to establish their possible rôle in arteriosclerosis. Since Goldblatt[39] emphasized that arteriosclerosis in the cow's aorta was never found to involve the intima but was limited to the media, the pathogenetic relationship of intimal capillarization to bovine arteriosclerosis was not pertinent. The course of capillaries has been followed from their origin in the vasa vasorum through the outer zone of the media in human vessels unaffected by arteriosclerosis.[40] An occasional capillary traversed the middle portion of the medial coat, but none were seen in the inner zone.[41] In the aorta of the horse and the dog, Woodruff[42] established a medial vascularization by injection of India ink and gelatin into the vasa vasorum. Gross and his coworkers,[43] and Horn and Finkelstein[6] denied the presence of any capillaries in the media of normal coronary arteries. It was our impression that if they did exist in healthy peripheral vessels they were infrequent. The nutrition of the wall of the normal vessel, because of the absence of vascularization, must be derived largely from the blood stream.[44] Anitschkow[11] showed evidence for this hypothesis by intravital trypan blue injection, in which the dye was seen to diffuse through the intact endothelium into the wall of the vessel.

In contradistinction to the absence of intimal vascularization in healthy arteries the presence of intimal blood supply in arteriosclerotic vessels has been well-recognized.[4, 45, 46] The origin of the mural capillary has long been a subject of controversy. Some investigators [37, 43, 47] claimed the vasa vasorum to be the more common source, while others[1, 2, 3, 12] felt that they rose chiefly from the main lumen of the vessel. By serial survey of ten representative sections we traced intimal capillaries back to the lumen of the vessel as well as to the vasa vasorum. From both sources there arose an intercommunicating anastomatic network of vascular channels. The distribution of the capillary network of the intima was particularly noted. It was most abundant in young

plaques where fresh organization occurred. It was least evident in areas of complete fibrosis. As the paths of the capillaries were traced through the media and internal elastic membrane, they were found to enter a relatively fresh area of granulation tissue. As the capillary approached a zone of dense fibrosis, it either skirted the area, terminated abruptly, or occasionally remained as a ghost-lumen filled with either a hyalinized or calcified thrombus. This gave the impression that the contraction of the scar had choked-off its own blood supply.

In the atheromatous abscess, capillaries were inconspicuous except in the periphery of the lesion. As they penetrated towards the necrotic center, necrosis occurred in their delicate thin walls. The nuclei and cellular outlines disappeared and were replaced by an eosinophilic granular structureless substance. Rupture resulted through the necrotic wall allowing extravasation of the blood elements into the atheroma.

In the vessels in which complete occlusion occurred, mural capillaries might assume a function other than that of nutrition. It was conceivable that they might constitute an attempt at intravascular collateral circulation. Winternitz and his coworkers[38] indicated the establishment of such a collateral channel by perfusion and injection technic. We attacked the problem by studying the stage of the thrombus and comparing the number of capillaries found therein with the number found within the wall of the main vessel. The mural circulation showed a rough relationship to the stage of occlusion. Old fibrotic, avascular occlusions showed an abundant mural vascularity; an attempt has been made within the wall of the vessel to shunt the blood flow around the occluded portion. Mural capillaries were less abundant in vessels which revealed extensive recanalization of the occluding thrombus; the recanalized channels within the thrombus assumed the burden of the circulation (Fig. 5). Roughly, an inverse ratio existed in the degree of capillarization between the luminal occlusion and the mural collateral response.

SUMMARY

(1) In 74 cases of gangrene of the lower extremity necessitating amputation, the vascular tree was studied in order to establish the pathogenetic events leading to occlusion and to classify the types of arterial occlusion. The rôle of mural hemorrhage was emphasized as the most frequent factor precipitating acute luminal thrombosis.

(2) A study of the atheroma, its capillarization, and the state of its stroma was reviewed to establish the fact that intimal hemorrhage was secondary to rhexis of the vascular channels traversing the necrotic atheroma.

(3) All types of occluding mechanisms were discussed in order to determine the importance of each. Arteriosclerosis with severe encroachment of the lumen was second in frequency to thrombosis upon athero-hematoma.

(4) A means of differentiating the fibrinoid substance from fibrin by trypsin digestion was described. A relationship between the fibrinoid substance

and partially degenerated collagen based on the results of trypsin digestion was entertained.

(5) Intimal and medial capillarization in arteriosclerotic vessels were traced to both the lumen and the vasa vasorum. Their reparative significance in the process of arteriosclerosis and their anastomotic importance in arterial occlusion were discussed.

(6) No difference was noted between the arteriosclerotic findings of the diabetic from the nondiabetic specimens.

BIBLIOGRAPHY

[1] Paterson, J. C.: Vascularization and Hemorrhage of the Intima of Arteriosclerotic Coronary Arteries. Arch. Path., **22**, 313, 1936.

[2] Paterson, J. C.: Capillary Rupture with Intimal Hemorrhage as the Causative Factor in Coronary Thrombosis. Arch. Path., **25**, 474, 1938.

[3] Wartman, W. B.: Occlusion of Coronary Arteries by Hemorrhage into Their Walls. Am. Heart Jour., **15**, 459, 1938.

[4] Winternitz, M. C., Thomas, R. M., and Le Compte, P. M.: The Biology of Arteriosclerosis. Baltimore, Charles C. Thomas, 1938.

[5] Leary, T.: Vascularization of Atherosclerotic Lesions. Am. Heart Jour., **16**, 549, 1938.

[6] Horn and Finklestein, L. E.: Arteriosclerosis of the Coronary Arteries and the Mechanism of Their Occlusion. Am. Heart Jour., **19**, 655, 1940.

[7] Boyd, A. N.: An Inflammatory Basis for Coronary Thrombosis. Am. Jour. Path., **4**, 159, 1928.

[8] Romeis, B.: Tashenbuch der mikroskopeschen Technick. München and Berlin, R. Oldenburg, 1924.

[9] Ewald, A., and Kuhne, W.: Die Verdauung als histologische Methode. Verh. Naturhist. med. zur Ver. Heidelberg, 1 (N.F.), 451, 1877.

[10] Saltykow, S.: Die Experimentelle Erzengengten Arterienveranderungun. Zentralbl. f. allg. Path. u. path. Anat., **19**, 321, 1908.

[11] Anitschkow, N.: Experimental Arteriosclerosis in Animals (Chap. **10** of Arteriosclerosis). Ed. E. V. Cowdry. New York, The Macmillan Co., 1933.

[12] Leary, T.: Experimental Atherosclerosis in the Rabbit Compared with Human (Coronary) Atherosclerosis. Arch. Path., **17**, 453, 1934.

[13] Aschoff, L.: Introduction to Arteriosclerosis. Ed. E. V. Cowdry. New York, The Macmillan Co., 1933.

[14] Leary, T.: Atherosclerosis—Special Consideration of Aortic Lesions. Arch. Path., **21**, 419, 1936.

[15] Duff, G. L.: The Nature of Experimental Cholesterol Arteriosclerosis in the Rabbit. Arch. Path., **22**, 160, 1936.

[16] Lange, F.: Studien zur Pathologie der Arterien insbesondere zur Lehre von der Arteriosklerose. Virchows Arch., **248**, 463, 1924.

[17] Zinserling, W. O.: Untersuchungen über Arteriosklerose. I. Über die Aortenverfettung bei Kindern. Virchows Arch., **255**, 676, 1925.

[18] Snapper, I.: Chinese Lessons to Western Medicine—Lecture at Mt. Sinai Hospital. New York, January 13, 1941.

[19] Leary, T.: Pathology of Coronary Sclerosis. Am. Heart Jour., **10**, 328, 1935.

[20] Allen, A.: So-called Mixed Tumors of the Mammary Gland of Dog and Man. Arch. Path., **29**, 589, 1940.

[21] Benson, R. L.: The Present Status of Coronary Arterial Disease. Arch. Path., **2**, 876, 1926.

[22] Clark, E., Graef, I., and Chasis, H.: Thrombosis of the Aorta and Coronary Arteries: With Special Reference to the "Fibrinoid" Lesions. Arch. Path., **22**, 183, 1936.

[23] Apitz, K.: Über den Bau Jungster Blut Plattchenthromben and den Einfluss des Novirudins auf ihre Entstehung. Zentralbl. f. allg. Path. u. path. Anat., **50**, 9, 1930.

[24] Veal, J. R.: The Pathological Basis for Intermittent Claudication. Am. Heart Jour., **14**, 447, 1937.

[25] Hunter, J.: Observations on the Inflammation of the Intimal Coats of Veins. Tr. Soc. Imp. Med. and Surg. Knowledge, **1**, 18, 1793.

[26] Neumann, E.: Die Pikrocarminfarbung und ihre Anwendung auf die Entzundungslehre. Arch. f. mikrosk. Anat., **18**, 5130, 1880.

[27] Mallory, F. B.: The Infectious Lesions of Blood Vessels. Harvey Lectures, 1912–1913. Philadelphia, J. B. Lippincott Co., 1913, p. 150.

[28] Jaeger, E.: Zur Pathologischen Anatomie der Thrombangiitis Obliterans bei Juveniler. Virchows Arch., **284**, 526, 1932.

[29] Aschoff, L.: Thrombose und Embolie. Verhandl. d. Deutsch. Gesellsch. f. Kreislaufforsch, 1934, p. 11.

[30] Zucker, P.: Über die Nekrose in der Arteriosclerotischen Platte und ihre Beziehung zum Atherom. Virchows Arch., **295**, 301, 1935.

[31] Mallory, F. B., and Parker, F.: Reticulum. Am. Jour. Path., **3**, 515, 1927.

[32] Bell, E. T.: Arteriosclerosis of the Abdominal Viscera and Extremities (Chap. **17** in Arteriosclerosis). Ed. E. V. Cowdry. New York, The Macmillan Co., 1933.

[33] Dietrich, K.: Beiträge zur Pathologie der Arterien des Menschen. Virchows Arch., **274**, 452, 1929.

[34] Blumgart, H., Schlesinger, M., and Zoll, P.: Angina Pectoris: Coronary Failure: Acute Myocardial Infarction. J.A.M.A., **116**, 91, 1941.

[35] Hines, E. A., and Barker, N. W.: Arteriosclerosis Obliterans. Am. Jour. Med. Sci., **200**, 717, 1940.

[36] Friedberg, C. K., and Horn, H.: Acute Myocardial Infarction Not Due to Coronary Artery Occlusion. J.A.M.A., **112**, 1675, 1939.

[37] von Glahn, W. C.: The Pathology of the Coronary Arteries in Diseases of the Coronary Arteries and Cardiac Pain. Ed. R. L. Levy. New York, The Macmillan Co., 1936.

[38] Winternitz, M. C., Thomas, R. M., and LeCompte, P. M.: Studies in the Pathology of Vascular Disease. Am. Heart Jour., **14**, 399, 1937.

[39] Goldblatt, H.: Book Review: Winternitz, M. C., Thomas, R. M., and LeCompte, P. M.: The Biology of Arteriosclerosis. Am. Heart Jour., **46**, 765, 1938.

[40] Martin, H.: Recherches sur la pathogènee des lésions Athéromateuses des Artères. Rev. de méd., Paris, **1**, 35, 1881.

[41] Robertson, J. F.: Vascularization of the Thoracic Aorta. Arch. Path., **8**, 881, 1929.

[42] Woodruff, C. E.: Studies on the Vasa Vasorum. Am. Jour. Path., **2**, 567, 1926.

[43] Gross, L., Epstein, E. Z., and Kugel, M. A.: Histology of Coronary Arteries and Their Branches in the Human Heart. Am. Jour. Path., **10**, 253, 1934.

[44] Bruening, F.: Die Ernabrung der Gefasswand. Klin. Wchnschr., **3**, 2282, 1924.

[45] Klotz, O., and Lloyd, W.: Sclerosis and Occlusion of the Coronary Arteries. Tr. Am. Med. Phys., **45**, 108, 1930.

[46] Ramsey, E. M.: Nutrition of the Blood Vessel Wall; Review of the Literature. Yale Jour. Biol. and Med., **9**, 13, 1936.

[47] Kaufman, E.: Pathology for Students and Practitioners. Translated by S. P. Reiman. Vol. I. Philadelphia, P. Blakiston's Son and Co., 1929.

[48] Boyd, W.: The Pathology of Interval Diseases. Philadelphia, Lea and Febiger, 1931.

[49] Eliason, E. L., and Wright, M. V.: Diabetic and Arteriosclerotic Gangrene of the Lower Extremities. Surg., Gynec. and Obstet., **42**, 753, 1926.

THE TREATMENT OF SEVERE STAPHYLOCOCCAL INFECTION WITH SPECIFIC TYPE-A ANTIBACTERIAL SERUM

HARRY G. MCNAMEE, M.D.

PHILADELPHIA, PA.

FROM THE PHILADELPHIA GENERAL HOSPITAL, PHILADELPHIA, PA.

ANALYSIS OF STATISTICS from various sources, both in this country and abroad, reveals that staphylococcal septicemia is an infection accompanied by high mortality. While the fatality rate varies from 60 to 95 per cent in the different studies recorded, the average must be accepted as 75 to 80 per cent. Despite numerous expedients introduced in the past to improve the statistics, it must be admitted that they have failed in their purpose. Nonspecific measures such as surgical drainage and supportive treatment, undoubtedly of value, are nevertheless insufficient in altering to any marked degree the number of individuals succumbing to this form of septicemia. The recent studies reported by Julianelle[1, 2, 3] on the classification of staphylococcus, and culminating in an experimental, therapeutic serum,[4] suggested the possibility that staphylococcic septicemia might be controlled by the administration of antibodies directed against the carbohydrate elaborated by the virulent (*i.e.*, for man) organisms. In his preliminary note, Julianelle[4] considered the data then available on treatment as inconclusive but encouraging. Eager to determine the therapeutic effectiveness of the antiserum, hereinafter designated as Type-A, arrangements were made with the Lederle Laboratories, of Pearl River, N. Y., to furnish serum for an experimental study in this hospital. The arrangements were made with Doctor Julianelle's consent and approval. The study has continued for about two years, and in the interval, 18 patients with verified staphylococcal septicemia, one with osteomyelitis and transient bacteremia, and three with pneumonia without positive blood cultures, have been treated with the serum.

Experimental.—The patients utilized in this study were not selected in any way. Regardless of age, duration of infection, clinical complications, or prognosis, they were accepted for serum therapy on the basis of severe infection, preferably with septicemia. Consequently, a broad variety of staphylococcic infections are represented in the present series. The organisms isolated from the patients were studied for mannite fermentation and type of carbohydrate. Every strain but one was *aureus*, all fermented mannite,[5] and all yielded, on acid extraction,[2] the Type-A carbohydrate.

Treatment consisted not only of administration of Type-A antiserum but also of whatever supportive care was indicated, and particularly whatever surgical measures appeared to be advisable at the time. Most of the patients had been under treatment with sulfonamide drugs previous to administration of serum, and in many instances this caused a more prolonged delay in

serum treatment than was desirable. That the sulfonamides had not been effective, however, was the judgment of the physician in charge, and, in fact, a paper now in press[6] suggests these compounds leave much to be desired in their effect on severe staphylococcal infection. In most of the cases in this study the drugs were discontinued with serum therapy; in a few, however, the drugs were given simultaneously in spite of our order that they be withdrawn. Because of the number dying, however, it may be that the drug was not of great importance in the recovery.

It may serve best the purposes of this communication if the complete data are consolidated in the form of tables, containing the more important details regarding clinical history and treatment of each individual. The only division of patients to be made is that based on ultimate survival or death. While no comment is made in the protocols concerning blood cultures, it may be well to say that each patient had repeated cultures, for the most part both in broth and in agar, with measured quantities of blood to determine the number of staphylococci per cubic centimeter. Septicemia was determined by repeated growth of staphylococci from the blood and by the colony count. On this basis, it can be said that except for three of the five patients with pneumonia, septicemia was established in every patient but one, and in that one the evidence suggests merely a transient bacteremia (Patient I. A., Table I). Supportive treatment also has been omitted from the tables since this varied from individual to individual and included whatever was regarded as an adjuvant to the patient's welfare.

ANALYSIS OF PATIENTS SURVIVING INFECTION

The data dealing with recoveries will be found in Table I.

It will be seen that ten patients treated with serum eventually survived the infection. The group consists of five males and five females, with ages varying from 20 months to 43 years. In four of the patients, the septicemia started by way of osteomyelitis, one of whom was further complicated by clinically recognizable myocarditis, subsequently confirmed by electrocardiographic studies. In patient S. S., with osteomyelitis of the left femur, serum treatment was delayed until the thirty-first day of illness and was administered by the intravenous (132 cc.) and intramuscular (30 cc.) routes. In addition to supportive treatment, it was found necessary to incise over the trochanter and to drill openings into the femur where necrosis was found. This resulted in adequate drainage. In patient J. T., with osteomyelitis of the right foot, ulna, scapula and left fibula, complicated by myocarditis, surgical drainage was performed at each of these foci as well as four metastatic, subcutaneous abscesses. Serum treatment began on the tenth day of illness, and consisted of three daily administrations of serum of 60 cc., each given intravenously. In patient T. N., there was an abscess of the face, parotid gland, and left hand, as well as an osteomyelitis of the right foot. After removal of a splinter in the left hand which may or may not have initiated the original infection, incisions were made over the left hand, right foot, and internal malleolus.

Serum was given both intramuscularly and intravenously over a period of nine days. The later injections of serum were given with difficulty because of increasing sensitivity in the child, and, in fact, serum sickness, in the form of urticaria, subsequently appeared. The fourth case was that of a sailor in the U. S. Navy, with osteomyelitis of all the bones of the left foot, and yielding a single positive blood culture during the period of observation. Serum therapy was given late in the disease and the indications are that no benefit was derived from this treatment. Surgically, a number of procedures were undertaken with eventual amputation of the left leg.

In four other patients, the infection was predominantly pulmonary. In two, the pneumonic process was primary, although postoperative in one; and in two others the pneumonia was secondary to a surface lesion. No positive blood cultures were obtained in three of these individuals; while in one (Patient W. H.) several consecutive, positive blood cultures were cultivated; the colony count before treatment in fact reaching as high as 145 colonies per cc. of blood. In patient R. R., the pneumonia appearing in the left upper lobe was secondary to a boil on the left elbow, and was rapidly followed by empyema. In this case, it is probable that despite the negative blood cultures, extension of the infection from the original focus to the lung may have been by way of the blood. Serum was not administered until the twentieth day, and consisted of 60 cc. on that day, and 40 cc. on the twenty-first and twenty-second day, all given intravenously. The process of recovery was aided by thoracostomy and open drainage on the twenty-first day of disease. Similarly, in Patient W. H., the original lesion was a cellulitis of the left hand with an abscess on the back, and subsequently there was a metastatic pneumonia of the left upper lobe. Drainage of the hand and back was accomplished by incisions. Serum was given over a period of seven days, at first intravenously and later intramuscularly. The total amount was 165 cc. The pneumonia appearing in Patient M. M. followed herniorrhaphy by two days. Recognized early as staphylococcal in etiology, sulfathiazole was given to a total of 54 Gm. over seven days, but the infection merely became intensified with the formation of multiple abscesses throughout both lungs. At this time, the prognosis seemed hopeless, but it was, nevertheless, decided to start serum therapy. She received 260 cc. intravenously over seven days. The final patient of this group, E. E., was a typical example of primary staphylococcic bronchopneumonia confirmed by roentgenologic and sputum studies which yielded pure culture of *Staphylococcus aureus*. Serum treatment was delayed until the eleventh day because the patient was under sulfathiazole therapy (74 Gm. during the interval). With no improvement in her general condition, it was decided to give serum instead. Two intravenous injections were given, 60 cc. on the eleventh day, and 40 cc. on the twelfth day. Twelve hours following the second injection, the temperature fell to normal and remained at that point during the patient's stay in the hospital. The effect of the serum in this group of patients has been particularly striking, the latter two being especially impressive.

TABLE I

SUMMARY OF RECOVERIES FOLLOWING ADMINISTRATION OF TYPE-A ANTISERUM

Patient	Color	Sex	Age	Chief Clinical Signs	Day Serum Given	Surgical Care	Total Serum Administered	Skin Test to Carbohydrates	Serum Sickness
S. S.	W.	M.	13 yrs.	Osteo. lft. femur. Septicemia	31st	Incision-trochanter. Drilled holes in femur	162 cc. over 9 days	Not done	Urticaria and joint pains
J. T.	W.	F.	9 yrs.	Osteo. rgt. foot, ulna scapula and lft. fibula. Myocarditis, metastatic skin abscesses. Septicemia	10th	Drainage of each osseous focus	180 cc. over 3 days	Positive	None
T. N.	W.	M.	21 mos.	Osteo. rgt. foot. Abscess of face, parotid, lft. hand. Septicemia	6th	Incision int. malleolus, rgt. foot, lft. hand. Showed splinter lft. hand	140 cc. i.v. and i.m. over 9 days	Positive	Urticaria
I. A.	W.	M.	43 yrs.	Osteo. all bones of lft. foot. Transient bacteremia	Chronic	Eventual amputation of leg	200 cc. i.v. over 5 days	Not done	None
R. R.	W.	M.	16 yrs.	Boil lft. elbow, pneumonia, l.u.l. Empyema. Septicemia, not verified	20th	Resection 3rd rib posteriorly	100 cc. i.v. over 3 days	Not done	None
W. H.	W.	M.	20 mos.	Cellulitis lft. hand. Abscess of back, rgt. foot. Pneumonia, l.u.l. Septicemia	4th	Drainage of lft. hand, back, rgt. foot	165 cc. i.v. and i.m. over 7 days	Neg.?	None
M. M.	W.	F.	42 yrs.	Postoperative pneumonia. Septicemia, not verified	18th	None	260 cc. i.v. over 7 days	Positive	Urticaria
E. E.	W.	F.	32 yrs.	Primary bronchopneumonia. Septicemia, not verified	11th	None	100 cc. i.v. over 2 days	Positive	Urticaria. Joint pains
E. B.	C.	F.	30 yrs.	Meningitis. Septicemia	6th	None	80 cc. i.v. over 2 days	Not done	None
L. D.	C.	F.	41 yrs.	Meningitis. Septicemia	15th	None	120 cc. i.v. over 3 days	Positive	Urticaria

Volume 115
Number 2

In the final two surviving patients the infection was primarily in the meninges. The one, E. B., was a colored woman, who, following an injury, developed all the signs of typical meningitis. Spinal fluid yielded staphylococci on culture and the cell count and protein content were characteristic of purulent meningitis. Serum treatment was started on the sixth day and consisted of two injections. The spinal fluid became sterile several days later. Recovery was complete and the patient was discharged on the sixty-third day following the onset. In the other, L. D., a colored female, also, the chief clinical signs were those of meningitis with positive cultures of hemolytic *Staphylococcus aureus* from both spinal fluid and blood. Serum treatment, started on the fifteenth day of illness, consisted of 120 cc. given over three days.

It may be well to point out that of the surviving patients, five, or 50 per cent, gave signs of serum sickness. This consisted of urticaria, and in two, joint pains were also present. In each, the condition was mild and responded promptly to symptomatic treatment. Skin tests to the Type-A carbohydrate as suggested by Julianelle[4] to measure the adequacy of serum treatment were conducted in six of these patients. In five, the test elicited a typical wheal and erythema reaction, while in the sixth patient, the test was negative on the two occasions performed, both before completion of serum treatment.

Twelve patients are recorded in this summary—four males and eight females. Another patient has been omitted from the tabulation because, although serum was given on the eighth and ninth day of infection, which included pericarditis, the physician in charge decided to discontinue serum and give sulfathiazole instead. The patient died 13 days later, so that under the circumstances it cannot be determined what effect the serum actually had or may have had. The ages varied from three weeks to 41 years, and the clinical conditions at the time of first examination were extremely severe, if not critical. Thus, six patients died within 72 hours after first being treated with serum, four, in fact, within 36 hours. In addition, seven patients presented clinically recognizable endocarditis, one pericarditis, and in one even sinus thrombosis was suspected clinically and later confirmed at autopsy. In all but three of the patients dying, postmortem examinations were made so that the ultimate diagnosis could be made with certainty.

In patient B. O. the chief clinical signs were endocarditis and meningitis. Serum was given intravenously on the ninth, tenth, and eleventh days of illness, 50, 25, and 15 cc. respectively. Death occurred on the following day before further serum could be given. Autopsy confirmed the diagnosis of endocarditis (on the mitral valve) and meningitis, and revealed further, hemorrhagic infarcts in the kidneys, spleen, and heart. Patient L. C., with osteomyelitis of the left tibia, pneumonia of both lungs, pyonephritis and endocarditis, was placed on serum treatment the sixth day of illness, receiving a total of 480 cc. intravenously over nine days. In addition, incisions were made over the periosteum of the tibia and the right ulna disclosed pus in both situations. Considerable supportive treatment was instituted as well.

The colony count ran consistently high, and on the tenth day of treatment the patient expired. Postmortem examination disclosed multiple abscesses of lungs, spleen, and kidneys and a vegetation on the tricuspid valve. Patient T. K., with indefinite portal of entry, presented on examination symptoms of endocarditis. Serum was given on the seventh, eighth, and ninth days, 60, 40, and 40 cc., respectively. On the tenth day, death occurred. Autopsy revealed a perforated interventricular septum, perforation and vegetation of the aortic valve, and hemorrhagic infarct of the spleen. In patient J. N. endocarditis followed postabortal endometritis. Serum was given on the fifteenth, sixteenth, seventeenth, and eighteenth days, 160 cc. in all. Death ensued on the eighteenth day. In addition to infection of the uterus and endocarditis, postmortem examination showed the presence of hemorrhagic infarcts of spleen and lungs. Following suprapubic prostatectomy, patient S. C. developed both pneumonia and endocarditis despite immediate treatment with sulfathiazole and later sulfadiazine. On the sixteenth day, 80 cc. of serum were given intravenously, and within 24 hours, the patient died. At autopsy, there was seen a vegetation on the mitral valve and extensive bronchopneumonia. Patient A. M. was admitted on the third day of illness in a stupor and with definite clinical signs of endocarditis. Serum was given intravenously, 120 cc., and within 24 hours the patient died. Autopsy revealed a vegetation on the mitral valve, a focal abscess on the left ventricle, abscesses of spleen and kidneys and petechial hemorrhages of the gastro-intestinal tract, skin, and conjunctivae.

The final patient in this group, W. T., showed early evidence of endocarditis without demonstrable evidence of the portal of entry, although a chronic prostatitis may have been the primary focus. Serum therapy was begun on the eleventh day of disease and was continued for four consecutive days, for a total dosage of 240 cc. The patient died on the fifteenth day of disease. Postmortem examination revealed mitral valvulitis, multiple abscesses of the viscera, prostate, and brain, and petechiae of skin and conjunctivae. The foregoing group of patients, complicated with endocarditis when first seen, was a particularly unfair trial for any treatment. This is at once apparent when it is realized that two of the seven died within 48 hours, and two within 72 hours, thus suggesting, immediately, that the patients were hopeless at the very start. The remaining patients, however, survived four, five, and ten days. The indications are that in endocarditis the prognosis is still hopeless even with the added treatment of specific antiserum.

Another patient presented pericarditis as the chief therapeutic difficulty. Thus, D. K. had multiple skin abscesses, pneumonia of the right upper lobe, and pericarditis; probably all secondary to a paronychia on the left thumb. Sulfathiazole had been used before serum therapy, without checking the infection. A roentgenogram of the right femur the day before death showed osteomyelitis with extensive necrosis of the bone. Surgical treatment consisted of repeated pericardial taps, and pericardotomy, with insertion of drain. From the eleventh to the nineteenth day antiserum was administered intra-

TABLE II

SUMMARY OF SERUM TREATED PATIENTS WITH FATAL STAPHYLOCOCCAL SEPTICEMIA

Patient	Color	Sex	Age	Additional Clinical Signs	Day Serum Given	Surgical Care	Total Serum Administered	Death Following Serum	Autopsy Findings
B. O.	W.	F.	23 yrs.	Endocarditis Meningitis	9th	None	90 cc. i.v. over 3 days	Within 72 hrs.	Meningitis; mitral valvulitis; infarcts kidneys, spleen, heart, G. I. tract and liver
L. C.	C.	F.	11 yrs.	Osteo. lft. tibia Pneumonia, lft. lung Pyonephritis Endocarditis, acute gangrenous prostatitis	6th	Incision periosteum lft. tibia, rgt. ulna	480 cc. i.v. over 9 days	10 days	Multiple abscesses, lungs, spleen, kidneys; vegetation tricuspid valve
T. K.	C.	F.	23 yrs.	Endocarditis—portal of entry unknown	7th	None	140 cc. i.v. over 3 days	72 hrs.	Perforated interventricular septum; perforations and vegetation aortic valve; infarct spleen
J. N.	C.	F.	24 yrs.	Postabortal endometritis Endocarditis	15th	None	160 cc. i.v. over 4 days	4 days	Infected uterus; endocarditis; infarcts lungs and spleen
S. C.	W.	M.	51 yrs.	Pneumonia Endocarditis	16th	None	80 cc. i.v.	24 hrs.	Extensive bronchopneumonia; vegetation mitral valve
A. M.	W.	M.	25 yrs.	Admitted in stupor Endocarditis	3rd	None	120 cc. i.v.	24 hrs.	Vegetation mitral valve; abscess lft. ventricle; multiple abscesses spleen and kidneys; petechial hemorrhages skin, conjunctivae, and G. I. tract
W. T.	W.	M.	30 yrs.	Chronic prostatitis? Endocarditis	11th	Exploration of perirenal area (no pus found)	240 cc. i.v. over 4 days	5 days	Mitral valvulitis; multiple abscesses of brain, spleen liver, pancreas, kidneys, adrenals, prostate, petechiae of skin and conjunctivae
D. K.*	W.	F.	5 yrs.	Multiple skin abscesses Pneumonia r.u.l. Pericarditis	11th	Pericardial taps Pericardotomy Resection 6th lft. costal cartilage, with drain	300 cc. i.v. over 8 days	18 days	Not done
B. B.	C.	F.	32 yrs.	Primary pneumonia r.m.l. and r.l.l.	16th	None	200 cc. i.v. over 9 days	10 days	Bronchopneumonia; multiple abscesses of rgt. lung
C. K.*	W.	F.	3 wks.	Abscess of gums Sinusitis (ethmoid and antra) Pneumonia. l.u.l.	18th	Incision rgt. tibia	10 cc. i.v.	24 hrs.	Not done
S. B.	W.	F.	16 yrs.	Chemosis lft. eye Abscesses lft. face Edema rgt. eye	5th	None	200 cc. i.v. over 4 days	4 days	Thrombosis lft. sinus; basilar meningitis, etc.
J. P.	W.	M.	8 yrs.	Painful, swollen rgt. shoulder Coma	4th	None	60 cc. i.v. over 1 day	36 hrs.	Not done

* Skin tests with carbohydrate were made only on these two patients—they were negative.

venously, a total of 300 cc. being given in all, but without avail. Autopsy was not allowed.

ANALYSIS OF THE FATAL CASES OF INFECTION

The data dealing with fatal cases will be found in Table II.

The remaining patients form a miscellaneous group. Thus, patient B. B., with primary pneumonia in the right middle and lower lobes, had been on sulfathiazole for one week. On the sixteenth day serum was started, and five injections, of 40 cc. each, were given over a period of nine days. The patient died several hours following the last treatment. At postmortem examination, the right lung was found to be riddled with abscesses. The infection in C. K. started as an abscess of the gums followed by pneumonia of the left upper lobe and involvement of the ethmoidal sinuses and maxillary antra. A single injection of serum was given on the eighteenth day and the child died on the following morning. No autopsy was allowed. Patient S. B. presented, on admission, abscesses of the left face, chemosis of the left eye, with edema of the right eye which apparently followed the "picking of a pimple" on her chin. Sinus thrombosis was suspected but not definitely diagnosed. On the fifth through the eighth day 200 cc. of serum were administered intravenously, with the patient becoming progressively worse. On the ninth day the patient died. The main pathologic findings were thrombosis of the left sinus, basilar meningitis, and infection of the petrous portion of the left temporal bone. The infection in J. P. was rapid and fulminating, the whole course covering five days. Unfortunately, permission for postmortem examination was not granted, and it, consequently, is not clear exactly what happened. The chief complaint was pain over the right shoulder, and the boy was in coma when admitted. Blood cultures made obvious the diagnosis of staphylococcal septicemia. A single injection of 60 cc. of serum was made on the fourth day of illness, and on the following morning the patient died.

The evidence offered by the fatalities occurring in this study indicates the unfortunate distribution of patients referred for treatment. Thus, only three of the 12 survived more than a week: L. C. and D. K. who had progressed to a hopeless state because of the cardiac lesions; and B. B. in whom the pneumonia had not responded to sulfonamides, and was already of 16 days' duration. Aside from any other element, that of time alone was a handicap, apparently impossible to overcome.

It may be of interest to offer a final analysis of Type-A serum therapy based on the chief clinical manifestation. These data have been reassembled in Table III.

Endocarditis formed the largest single group with seven patients, all of whom died; pneumonia comprised the next largest with five, only two of whom had concurrent septicemia, and four of them recovered; osteomyelitis contributed four patients, three with septicemia and one with transient bacteremia, and all recovered; meningitis with septicemia was encountered twice, and both patients recovered. The remaining four patients, all with

* Skin tests with carbohydrate were made only on these two patients—they were negative.

TABLE III

SUMMARY OF SERUM TREATED CASES BASED ON CHIEF SYMPTOM

Chief Clinical Manifestation	Number of Patients			
	Treated	With Septicemia	Survived	Died
Endocarditis	7	7	0	7
Pneumonia	5	2*	4	1
Osteomyelitis	4	3	4	0
Meningitis	2	2	2	0
Pericarditis	1	1	0	1
Sinus thrombosis	1	1	0	1
Sinusitis with metastatic pneumonia	1	1	0	1
Undetermined septicemia	1	1	0	1
Totals	22	18	10	12

* Of these, one survived and one died.

septicemia, represented a scattering of diagnoses, and all died. The evidence suggests, therefore, that Type-A antiserum offers the most effective assistance toward recovery in pneumonia, osteomyelitis, and possibly in meningitis. In the cardiac complications—endocarditis or pericarditis—the serum appears to be valueless, if survival is taken as a criterion. The remaining cases are too few to allow comment.

Discussion.—The foregoing data reveal that 22 patients with severe staphylococcal infection have been treated with specific Type-A antibacterial serum. Bacteriologically, the different infections were associated with a single immunologic type, since all the strains fermented mannite and elaborated Type-A carbohydrate. This suggests that these infections may be treated logically with a univalent serum.

In every patient serum therapy was supplemented by whatever surgical and supportive care was indicated. On this basis ten of the 22 patients survived, and 12 died, indicating a therapeutic effectiveness of roughly 45 per cent or, stated differently, approximately a two-fold increase in the average survival rate usually accepted for such infections. As the figures now stand, it seems that pneumonia, osteomyelitis, and possibly meningitis respond most favorably to the action of Type-A serum.

Analysis of the deaths in this study suggests that the rate of recovery may be an inaccurate expression of the true capacity of the antiserum. The cardiac complications, for example, numbering eight out of 22 (about 37 per cent), or from the point of view of deaths, eight out of 12 (about 66 per cent) indicate, immediately, the particularly abnormal run of patients in this study. Examined in another way, nine of the 12 deaths (75 per cent) occurred within five days following the use of serum. In the light of such a disproportionately large number of patients with hopeless prognosis, it may be that the antiserum possesses a greater therapeutic efficiency than is actually observed in this study.

The skin test with carbohydrate, suggested as an index of sufficient serum therapy, was made in too few patients to be of statistical value. It may be that as far as the results go, however, they confirm its prognostic use. Of

the patients who recovered, the test was positive in five of six; and in the sixth, the last test was made before completion of serum administration. Of the patients who succumbed, the test was negative in three of three cases tested.

SUMMARY AND CONCLUSIONS

(1) Twenty-two patients with severe staphylococcal infection have been treated with Type-A anticarbohydrate serum supplemented with whatever surgical and supportive care seemed advisable.

(2) The strains of staphylococcus isolated in this study fermented mannite and elaborated Type-A carbohydrate.

(3) Of the 22 patients treated as described, ten survived infection and 12 died.

(4) Of the survivals, four were examples of osteomyelitis, four pneumonia, and two meningitis.

(5) Of the deaths, seven were examples of endocarditis, while the remaining were single cases of pneumonia, pericarditis, sinus thrombosis, sinusitis with metastatic pneumonia, and one, not examined at autopsy, of not too clear a diagnosis other than septicemia.

(6) Of the 12 deaths, six occurred within 72 hours, three others within five days, two within ten days, and one within 18 days after first using serum.

(7) While the group treated is small, the indications are that Type-A antiserum has a certain value in the treatment of severe staphylococcal infection, with the best results in this study in osteomyelitis and pneumonia, and the poorest results in cardiac infection.

It is a pleasure to acknowledge the assistance and cooperation received from the Lederle Laboratories, Dr. L. A. Julianelle, of Washington University, St. Louis, and Drs. W. G. Turnbull and J. H. Clark of this hospital.

REFERENCES

[1] Julianelle, L. A., and Wieghard, C. W.: Immunological Specificity of Carbohydrates Derived from Staphylococci. Proc. Soc. Exp. Biol. Med., **31**, 947–949, 1934.

[2] Julianelle, L. A., and Wieghard, C. W.: The Immunological Specificity of Staphylococci. I. The Occurrence of Serological Types. Jour. Exp. Med., **62**, 11–21, 1935.

[3] Wieghard, C. W., and Julianelle, L. A.: II. The Chemical Nature of the Soluble Specific Substances. *Ibid.*, **62**, 22–30, 1935.

[4] Julianelle, L. A.: Observations on the Specific Treasment (Type-A Antiserum) of Staphylococcal Septicemia. Ann. Int. Med., **33**, 308–316, 1939.

[5] Julianelle, L. A.: Determination of Staphylococcal Types by Fermentation of Mannite. Proc. Soc. Exp. Biol. Med., **36**, 117–119, 1937.

[6] Torrey, R. G., Julianelle, L. A., and McNamee, H. G.: The Sulfonamide Therapy of Staphylococcal Septicemia. Ann. Int. Med., 1941 (in press).

ERRATUM

In the ANNALS OF SURGERY, 115, 47, January 1942, the title of the article by Dr. Herman Charache should read "METASTATIC TUMORS IN THE BREAST." The word "METASTIC" is a typographic error.

BRIEF COMMUNICATION

DISARTICULATION OF THE HIP FOR ENDOTHELIOMA (EWING'S TUMOR): 31-YEAR FOLLOW-UP

BEVERLY CHEW SMITH, M.D.
NEW YORK, N. Y.

THE FOLLOWING is a report of an Ewing's tumor of the femur operated upon in 1909, and still without recurrence 31 years later. So far as is known, it is the only case of its kind in which so long a period of survival has been recorded. The case is registered with the Bone Sarcoma Registry of the American College of Surgeons, and the original pathologic sections of the tumor have been reviewed by a large number of pathologists, consultants of the Bone Sarcoma Registry, who have agreed as to the diagnosis of Ewing's tumor.

Case Report.—Presbyterian Hospital, Vanderbilt Clinic Unit No. 249752; Bone Sarcoma Registry No. 398: H. J., male, Russian Jew, age 22, was admitted, July 22, 1909, complaining of pain in the left thigh of five months' duration. In February, 1909, he first noticed a "squeezing" pain in the medial aspect of the left thigh. It was localized, nonradiating, and not severe. It grew gradually worse, however, with intermittent exacerbations, not provoked by any known activity. Three weeks before admission it had become more severe on walking, and spread from the medial to the anterior aspect of the middle third of the thigh. At times it radiated down the leg to the ankle. It was worse at night. The function of the knee was normal, and flexion and extension of the joint without weight-bearing did not increase the pain.

There were no other symptoms; there had been no injury to the thigh, no operations, and the patient denied venereal disease. His only childhood illness had been measles. He did not use alcohol, tobacco, tea or coffee. There was no history of tuberculosis or malignancy in the family.

Physical examination revealed a well-nourished, muscular young man, with no significant findings other than the local lesion in the middle third of the left thigh. This lesion was a palpable mass, about 6x8 cm., which was bony-hard, immovable, nontender, except to deep pressure, and was apparently attached to the femur. The overlying skin was normal. *Clinical Diagnosis:* Sarcoma of the femur.

Roentgenograms, unfortunately, since destroyed, are said to have shown slight thickening of the periosteum about the center of the shaft of the femur, particularly on its medial aspect. The lesion was regarded as chronic periostitis, associated with osteomyelitis, and operation was not advised. The patient was discharged, July 27, 1909, to report to the Out-Patient Department for observation.

One month later he was readmitted. Since his discharge the pain had increased in intensity and frequency. There was no interference with function other than a sense of insecurity in the thigh, but the pain was so severe that it prevented walking. The mid-left femoral region was now obviously larger than the right.

The findings on physical examination were essentially the same as on the first admission. The reflexes in the lower extremities remained normal. There was no edema. In the midthird of the left femur a hard, smooth mass could be felt. It had not grown appreciably, was not especially tender, and apparently did not involve the overlying muscles or skin. On August 26, 1909, operation was undertaken by Dr. John Hartwell, with a preoperative diagnosis of chronic periostitis of the femur, and a possibility of periosteal sarcoma. The white blood count was 8,750, with 79 per cent polymorphonuclears, and no abnormal white cells.

The tumor was approximately four inches long and occupied the internal, anterior and posterior aspect of the bone. It was fibrous, gristly and attached to the periosteum and underlying bone, from which it was chiseled away *en masse*, leaving a roughened underlying bone surface. It is the reporter's impression that the medullary cavity was not entered. The tumor was soft in places, with plaques of bony-hard substance. It was not obviously vascular and contained no pus.

The postoperative course was uneventful, and the patient was discharged September 17, 1909, 22 days after operation. Coley's serum was administered postoperatively.

Pathologic Report.—No. 6689: This described the tumor as a bony neoplasm, containing, on the under surface, a milky exudate, apparently softened new growth. Microscopically, it consisted of atypical bone without any haversian systems. It was infiltrated with large cells with large vesicular nuclei and scanty protoplasm, appearing in masses between the spicules of bone. Mitotic figures and multinucleated cells were common. *Pathologic Diagnosis:* Large round cell sarcoma.

Following discharge the patient was admitted to Memorial Hospital for further treatment with unfiltered Coley's toxin. Beginning with one minim, on November 9, 1909, injections were given in the thigh or buttock almost daily, in increasing doses until on November 30, 1909, the patient received 14.5 minims. Treatment was then discontinued for six days but was resumed on December 7, 1909, and continued until December 13, 1909. Altogether the patient received a total of 197 minims in addition to the 16 doses previously given at the Presbyterian Hospital. At the Memorial Hospital, from December 14, 1909, until his discharge on December 20, 1909, the patient suffered greatly with pain in his left thigh, headache, and backache, requiring morphine for relief. On December 15, 1909, the white cell count was 14,000, with 86 per cent polymorphonuclear leukocytes.

The patient was readmitted to the Presbyterian Hospital, December 21, 1909, complaining of pain in the thigh, which was constant, and nonradiating; it had grown steadily worse and the thigh had noticeably increased in size. A hard, bony, tender fusiform swelling occupied the midthird of the internal and anterior aspects of the left thigh. The skin and muscles were freely movable over the mass. There was no fluctuation. Over the tumor the thigh measured 47 cm. as compared with 43 cm. for the opposite thigh. The knee joint was held in a slightly flexed position and could not be straightened voluntarily. The popliteal space was negative and the dorsalis pedis artery was palpable. No palpable lymph nodes were discovered. *Clinical Diagnosis:* Sarcoma of the left femur.

On December 23, 1909, disarticulation of the left leg through the hip joint was performed by Dr. Joseph Blake. On removing the extensor muscles of the thigh a soft oval tumor, 12x7 cm., was exposed. Its cut-surface was gelatinous and varied in color from pale pink to dark red. It was very friable, and, adjacent to the bone, imparted a gritty sensation. It was firmly adherent to the bone and appeared to spring from the periosteum.

Microscopically (Path. No. 10087), the tumor was found to be composed of medium-sized round cells, closely packed together and supported by very little stroma. Blood vessels lay in intimate contact with the cells which radiated from the vessel walls in a manner suggesting that they originated from the vessels. Large spaces in the tumor contained necrotic tissue and leukocytes. *Pathologic Diagnosis:* Round cell sarcoma (perithelioma).

Dr. A. P. Stout has recently reviewed the sections of the tumor and reports as follows: "Sections show that the tumor is composed of long cords of cells, which are usually solid and are separated from one another by strands of fibrous tissue. In a considerable number of instances there is a capillary in the center of a fibrous tissue strand. The fibrous tissue in every instance separates the capillary from the tumor cells. Where the tumor masses are large, the cells, at the greatest distance from the capillaries, are necrotic. The section shows a few spicules of bone. Most of these, in turn, are necrotic, due apparently to pressure from the massed tumor cells which fill the marrow spaces. A few of the spicules suggest new formation of bone. In every instance this is

an irritative and not a neoplastic type of proliferation. The individual tumor cells are, for the most part, rounded, averaging 20 microns in diameter. The nucleus is hyperchromatic, but the nucleoli are, for the most part, small and inconspicuous. Mitoses average one in every high-power field, and in some regions are more frequent than this. The nuclei are centrally placed and are surrounded by thin zones of cytoplasm, which is palely stained and inconspicuous. So far as one can tell from the hematoxylin-eosin stain, there are few or no fibers accompanying the tumor cells except for the broad septa which separates the cords of cells. This picture is characteristic of the bone marrow tumor, variously classified as reticulocytoma, endothelial myeloma, and Ewing's tumor. *Pathologic Diagnosis:* Ewing's tumor of the femur."

Subsequent Course.—The patient left the hospital February 4, 1910, and four months later resumed his work as an engraver. He was then lost sight of until October 2, 1922, when an insurance company, to whom he applied for insurance, requested a report of the hospital findings. The patient has since been followed continuously. Repeated examinations have revealed no evidence of recurrence clinically or roentgenographically. In April, 1937, he began treatments in the Metabolism Clinic for diabetes, which he had recently developed. This has since been controlled under a dietetic regimen.

SUMMARY

A case of Ewing's tumor of the femur is presented, with survival without recurrence 31 years after the patient first presented himself for treatment.

DISCUSSION.—DR. BRADLEY L. COLEY (New York) said that Doctor Smith's case was unique. There are no other cases on record in the Bone Sarcoma Registry of a proven endothelioma of bone that has survived, as this one has, for a period of over 30 years. Furthermore, there are only 11 such cases in the entire Registry that have survived for five years or more.

As far as treatment is concerned, in the present case both surgery and Coley's toxins were employed. The late Dr. William B. Coley was very much interested in this patient and presented him on several occasions. It was his feeling that the toxins played a definite part in the prevention of distant metastases. In this connection, it might be of interest to mention that of the 11 five-year survivals of endotheliomata of bone listed in the Bone Sarcoma Registry, six received toxins. In this group, of which six were males and five were females, there were no five-year survivals following the use of radiation alone, or toxins alone. In only two instances were surgical measures alone employed. Three were treated by surgery and radiation, one by surgery and toxins, one by radiation and toxins, and four by surgery plus radiation and toxins.

The patient is free of signs and symptoms of local or distant persistence of this tumor on December 1, 1941, thirty-two years after operation.

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY

Walter Estell Lee, M.D.
1833 Pine Street, Philadelphia, Pa.

Contributions in a foreign language when accepted will be translated and published in English.

Exchanges and Books for Review should be sent to James T. Pilcher, M.D., Managing Editor, 121 Gates Avenue, Brooklyn, N. Y.

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY
East Washington Square, Philadelphia, Pa.